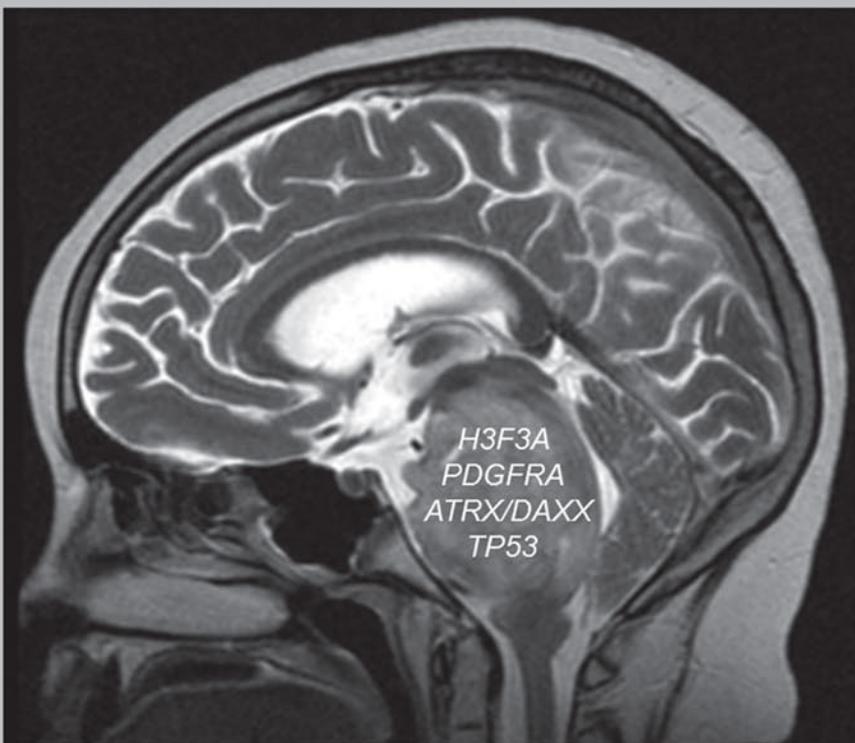
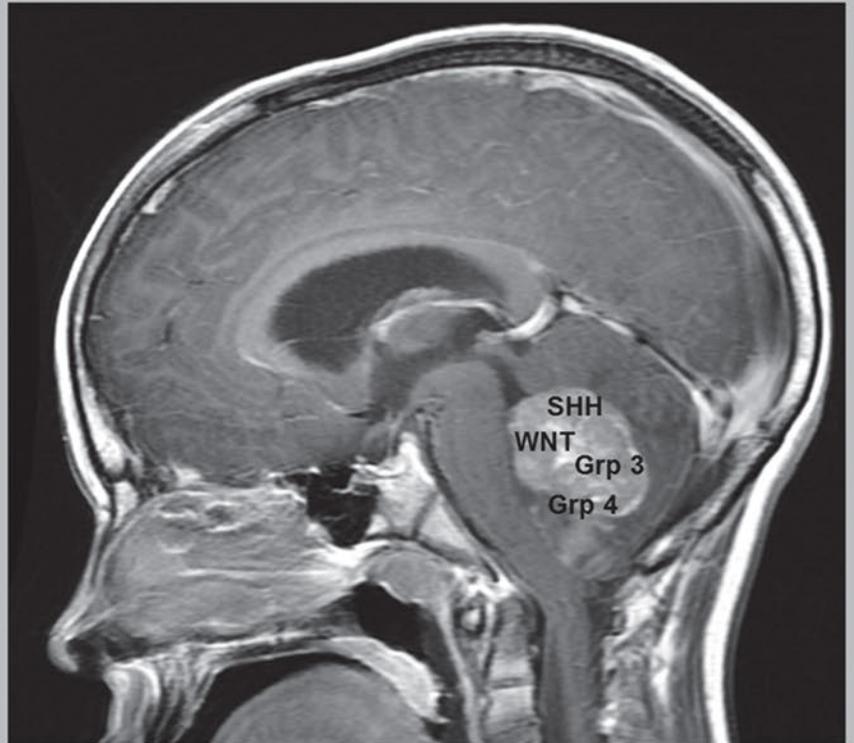


Principles and Practice of Pediatric Neurosurgery

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3rd Edition



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This book is dedicated to

Susan Ferson, Julie and Todd Albright

Connie, Benjamin, and Andrew Pollack

Barbara, Samuel, and Richard Adelson; Casey, Brittany, and David Biederman

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Preface

It was our hope that the first edition of this book would help improve the care of children with pediatric neurosurgical disorders and would contribute to the education of their caregivers. We have been gratified by the widespread acceptance and use of both the first edition in 1999 and the second edition in 2007, and particularly gratified by its increased use throughout the world.

In 2011, we began work on the third edition, with the same objectives as for the first edition. Organization of the book remains the same: general topics, congenital and developmental cerebral disorders, congenital and developmental spinal disorders, neoplasms, trauma, cerebrovascular disease, functional disorders, infectious disorders, and neuroanesthesia. The third edition, however, differs from the second edition in several ways. This edition includes seven chapters not included in the second edition: caring for the pediatric neurosurgical patient, cellular therapy for pediatric neurosurgical disease, conjoined twins, lipomeningoceles, skeletal syndromes, radiotherapy of brain tumors, and Moyamoya disease. The chapter on caring for the pediatric neurosurgical patient is likely to be of value daily.

We continued to invite acknowledged authorities to contribute chapters and attempted to identify individuals with balanced judgment and experience. Most of the chapters achieved that goal. Readers will note that 42 of the 82 chapters in this edition were written by different authors than the second edition—a fact that represents primarily the maturation of younger pediatric neurosurgeons into established authorities. Only 29 authors in this edition contributed to the first edition. Readers will also note that chapters in this

edition were written by authors in Europe (Richard Hayward and Dominic Thompson), the Middle East (Schlomi Constantini), and Africa (Anthony Figaji and Graham Fieggen)—a fact that acknowledges the international readership of the book, but more importantly, the international expertise about those topics.

The cover illustration—a magnetic resonance scans of a pediatric medulloblastoma and a diffuse intrinsic brainstem glioma (DIPG)—is similar to illustrations on the covers of the first two editions of the text, but includes genetic markers of those tumors that were unknown in 2007 and that have the potential to further improve the prognosis of children with medulloblastomas, and to perhaps finally improve—to at least a measurable extent—the terrible prognosis of children with DIPG.

When comparing the content of this third edition with that of the first, it is clear that pediatric neurosurgeons are able to give better care to children with many neurosurgical disorders, and far better care to those with a few disorders. It is also clear that for several classical pediatric neurosurgical disorders, such as myelomeningoceles and encephaloceles, little has improved since the first edition (other than the benefits of *in utero* closures) and to note that their incidence has steadily declined in developed countries, so that evaluation of prevention and treatment is less feasible.

Pediatric neurosurgeons, in general, are grateful for the blessing of caring for children with the disorders described on the following pages. We three editors remain hopeful that this third edition will help to further improve their care.*

* Note about the cover images: Sagittal magnetic resonance images of pediatric medulloblastoma (lower left) and diffuse intrinsic pontine glioma (DIPG, upper right). For the former tumors, recent studies have demonstrated the existence of at least four molecularly defined tumor subgroups, currently referred to as Shh, Wnt, Group C, and Group D, which have provided new insights regarding risk stratification and treatment planning. For DIPGs, which have proven resistant to conventional chemotherapy and radiotherapy approaches, recent molecular data has demonstrated frequent alterations in histone modification genes and *PDGFRA*. Time will tell whether these insights will translate into improvements in response and survival for children with these challenging tumors.

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- 1 The History of Pediatric Neurosurgery
- 2 Normal and Abnormal Development of the Nervous System
- 3 Neurologic Examination of the Newborn, Infant, and Child
- 4 Caring for the Pediatric Neurosurgical Patient
- 5 Pediatric Neurosurgery in Developing Countries
- 6 Ethical Issues in Pediatric Neurosurgery
- 7 Applications of Cellular Therapy in Pediatric Neurosurgery

1 The History of Pediatric Neurosurgery

R. Michael Scott

1.1 Introduction

The beginning of the subspecialty of pediatric neurosurgery is perhaps best documented in a letter, currently in the possession of the Chief of Pediatric Neurosurgery at the Boston Children's Hospital, written by Harvey Cushing in 1929 to a woman requesting care for her child with a probable brain tumor: "the right thing is to have you take him to see Dr. [Franc] Ingraham at the Children's Hospital, and to abide unequivocally by what he says." Over the next 30 years, neurosurgeons around the world began to devote major parts of their practice to the care of infants and children with neurosurgical disorders, and by the early 1950s, dedicated pediatric neurosurgical services were being established in the world's major cities, including Boston, Buenos Aires, Chicago, London, Paris, Philadelphia, and Toronto, to name just a few. A major reason for the development of these services was the increasing prominence of prestigious children's hospitals staffed by committed pediatric subspecialists in all areas of medicine and surgery, who were founding world-renowned services in their own specialties. It was only natural that pediatric neurosurgery would come into its own, driven by similarly committed neurosurgeons and institutions influenced by dedicated pediatricians, subspecialists, and hospital administrators, who wanted only the best-trained neurosurgical specialists to care for their patients. As Robin Humphreys pointed out in the earlier edition of this chapter, however, many neurosurgeons who specialized in the care of pediatric patients continued to have simultaneous adult practices through the 1960s and 1970s. At the time of this writing (2012), however, there are now several hundred neurosurgeons in the United States and Canada whose practices are limited to pediatric patients, and who practice exclusively in pediatric hospitals. How did this change come about?

One of the major influences on the development of our subspecialty was the publication of influential textbooks that outlined the presenting signs and symptoms of pediatric neurosurgical disorders, their diagnosis, and their surgical management. The anatomy and treatment of many congenital anomalies were difficult to understand, given the limitations of imaging before the development of computed tomography (in the 1970s) and magnetic resonance imaging (in the 1980s), and the rarity of many of these conditions; an experienced pediatric surgeon's delineations of these conditions via a text was often the only way of advancing knowledge in the field of neurosurgery. The medical publisher Charles C Thomas published many short, themed monographs on conditions like medulloblastoma and spina bifida, and many pediatric case series were published in our journals, particularly the *Journal of Neurosurgery*, but it was not until the pivotal *Neurosurgery of Infancy and Childhood*,¹ by Franc D. Ingraham and Donald D. Matson, published in 1954, that any such compendium was available for the interested neurosurgeon or resident. The second edition, now authored

solely by Matson, was published in 1969,² and it became the authoritative pediatric neurosurgical text for many of us in training or in practice during that era; many of Matson's diagnostic aphorisms remain relevant even today. The text remains a fascinating window into the treatment strategies of the pediatric neurosurgeon practicing in the middle of the 20th century. Other texts were published over the next two decades, but as pointed out by Robin Humphreys, quoting the comments of Kenneth Till, it was not until pediatric neurosurgeons "began to discover one another"^{3,4} and to discuss mutual interests that this special area of neurosurgery began to flourish and subspecialty societies began to form to encourage the exchange of ideas and promote better care for the pediatric neurosurgical patient.

In the first edition of this chapter, Dr. Humphreys canvassed pediatric neurosurgeons at some of the oldest and most established pediatric neurosurgical centers in the world to record their histories for posterity, and I have quoted liberally from his initial chapter depictions in the sections that follow.

1.2 Program Development and Institutional Histories

1.2.1 Australia (E. A. Lewis, MD and D Simpson, MD, Written Communications to Dr. Humphreys, October 2004)

The development of pediatric neurosurgery from its general neurosurgery roots is well illustrated by its evolution in Australia. General surgery arrived with the first fleet in 1788, but it was more than 100 years before the first successful adult neurosurgical cases were undertaken. The grandfathers of pediatric neurosurgery in Australia, like those in many other countries, had obtained their initial experience in other disciplines. T. Y. Nelson, a general pediatric surgeon, and his pupil, Marcel Sofer Schreiber, were perhaps the earliest practitioners of children's neurosurgery in Sydney. Reginald Hooper, who in the late 1950s was appointed to the Royal Children's Hospital, took the lead in Melbourne. Donald Simpson had been working in Adelaide since 1949; by 1956, he had established a relationship with the Adelaide Children's Hospital.

The Australian neurosurgical community also felt Donald Matson's influence when Matson visited that country in 1966, by which time freestanding children's hospitals located in the country's capital cities had been established. Then, as now, the challenge was the provision of "high-quality service over the tyranny of distance" (E. A. Lewis, MD, written communication to Dr. Humphreys, October 2004). Today, there are neurosurgeons specializing in pediatric neurosurgery throughout Australia and New Zealand.

1.2.2 Boston, Massachusetts—Boston Children’s Hospital

“If anyone can lay claim to be the father of pediatric neurosurgery, it would be Franc Ingraham.”⁵ Born in 1898, Ingraham entered Harvard Medical School in 1921 and received his medical degree 4 years later. He then spent 3 years with Harvey Cushing, 1 year in surgical research at Johns Hopkins, and an additional year working with Sir Charles Sherrington in the physiology laboratories at Oxford. Returning to Boston from England in 1929, Ingraham, with his extensive clinical and investigative background, focused on the rapidly expanding area of neurologic surgery for children at Cushing’s request.⁶ As noted earlier in this chapter, he started a pediatric neurosurgical service at Boston Children’s Hospital that to the author’s knowledge was the first of its kind. Generations of pediatric neurosurgeons in America and throughout the world were the benefactors of either his tutelage or that of his pupil, co-worker, and successor, Donald Matson. Over 40 neurosurgeons came to Boston Children’s Hospital to spend extended periods of time learning this new subspecialty, and many of them became chairpersons of their own departments or directors of their own pediatric neurosurgical services in academic institutions throughout North America and the world. Ingraham and his colleagues described the diagnosis and treatment of such clinical entities as subdural hematoma during the first 2 years of life,⁷ subdural effusions complicating bacterial meningitis in infancy,⁸ premature closure of cranial sutures,⁹ diastematomyelia,¹⁰ persistent dermal sinus tracts, and other variations of congenital spina bifida,¹¹ as well as the classification and treatment of hydrocephalus.¹¹ Ten years before his 1954 text with Matson, Ingraham had published *Spina Bifida and Cranium Bifidum*.¹² Matson and Ingraham’s collaboration sadly ended with Ingraham’s death in 1965 and Matson’s demise 4 years later of Jakob-Creutzfeldt disease.

1.2.3 Buenos Aires, Argentina (G. N. Zuccaro, MD, Written Communication, January 2005)

Raul Carrea was perhaps the first dedicated pediatric neurosurgeon in Argentina, beginning neurologic research when he was a student. In the mid 1940s, he worked with Pio del Rio Ortega. Shortly afterward, he continued his training as a Commonwealth Fund fellow in New York at Columbia University, where he worked both in neurophysiology research and in neurosurgery. Following his return to Buenos Aires, Carrea developed his neurosurgical career at the Cancer Institute Angel H. Roffo and at the Ricardo Gutierrez Children’s Hospital. Although this hospital had been founded in 1875, there was no designated neurosurgeon; general surgeons operated on the sporadic neurosurgical cases. At that institution, Carrea in 1956 created the first Department of Pediatric Neurosurgery, with its own special ward, an associated neuroradiology facility, and operating rooms. It was the first such department in Argentina. Subsequently, he created the first residency program in neurosurgery

at the Children’s Hospital based on his belief in the need for specialized training.

Carrea’s interest in the treatment of hydrocephalus resulted in the imaginative strategy of deviating obstructed cerebrospinal fluid to the mastoid air cells, thereby saving the lives of many children at a time when shunt systems did not exist. Eventually, he designed his own shunting system, but the cost restricted its accessibility to families with means. The budget restrictions at the Children’s Hospital prompted Carrea to organize a group of parents and wealthy friends to create the Foundation for the Fight against Neurological Diseases in Childhood (FLENI). The foundation flourished under his leadership, and his department of neurosurgery became a state-of-the-art center that still has an international reputation in the field of neurologic diseases.

1.2.4 Cape Town, South Africa—Red Cross War Memorial Children’s Hospital

The Department of Neurosurgery in Cape Town was established in 1946 by Hermann de Villiers Hammann, a South African trained in Germany.^{13,14} As a rule, children were operated on by general neurosurgeons until 1970, when Professor J. C. (Kay) de Villiers was appointed as the first full-time academic neurosurgical head in Cape Town. He quickly recognized that there was a need to establish pediatric neurosurgery as a subspecialty; this decision was facilitated by the fact that Cape Town had the only freestanding pediatric hospital in South Africa. The Red Cross War Memorial Children’s Hospital had been established after the Second World War with contributions from the citizens of Cape Town, given in memory of those fallen. De Villiers developed a combined spinal dysraphism clinic, which he ran assisted by personnel from the orthopedic and urology departments. In the years that followed, the first full-time academic pediatric neurosurgical post was created at the Children’s Hospital, and the hospital became the referral center for most of southern Africa.

1.2.5 Chicago, Illinois—Children’s Memorial Hospital (D. G. McLone, MD, Written Communication to Dr. Humphreys, June 2004)

Neurosurgery was established at Children’s Memorial Hospital in 1950 by Luis Amador, who must have been influenced by the presence of Paul Bucy and Percival Bailey at Northwestern University. Amador, described as a true academic and technically skilled surgeon, held only a part-time appointment at Children’s Memorial Hospital, which was typical for that era. During that decade, he accepted international trainees, such as Kenneth Till and Sanat Bhagwati, for additional experience in pediatric neurosurgery; this training opportunity for neurosurgeons from around the world was to become a consistent feature of the pediatric neurosurgical service at Children’s Memorial Hospital during the years that followed. Bhagwati, training

with both Till and Raimondi, went on to spearhead the development of pediatric neurosurgery in India, where over 150 neurosurgeons now devote most of their practice to the care of pediatric patients.¹⁵

Meanwhile, Anthony Raimondi, born and raised in Chicago but schooled in medicine at the University of Rome, had completed his neurosurgical residency with Joe Evans at the University of Chicago.¹⁶ During this time, Raimondi had an opportunity to study pediatric neurology under Douglas Buchanan. This experience doubtlessly contributed to his decision to dedicate his life to pediatric neurosurgery. In what would now be considered a fellowship, Raimondi worked with Amador at Children's Memorial Hospital. In 1963, when he was 34 years old, Raimondi went across town to the Cook County Hospital. Although his responsibility was primarily the care of adult patients, he was still absorbed by the surgical disorders that affect a child's nervous system. He was intrigued by the potential of cerebrospinal fluid shunt systems as well as the utility of cerebral angiography as a diagnostic tool in children.

In 1968, Bucy prevailed upon Raimondi to return to Children's Memorial Hospital as Chairman of Pediatric Neurosurgery, and Raimondi subsequently became Professor and Chairman of Neurosurgery at Northwestern University. As an educator, Raimondi did not disappoint the university. As a testament to Raimondi's passion for the training of many young neurosurgeons (at least 25 of whom were from Japan alone) and the promotion of continuing education programs in pediatric neurosurgery, five of his former students have served as presidents of the International Society of Pediatric Neurosurgery.

1.2.6 Edinburgh, Scotland—Royal Hospital for Sick Children (A. J. W. Steers, MD, Written Communication to Dr. Humphreys, July 2004)

Not long after he qualified as a doctor in 1919, Norman McOmish Dott received a Rockefeller Fellowship to study at Peter Bent Brigham Hospital, where he was appointed as a junior associate in surgery to Harvey Cushing.¹⁷ "In one of his letters, Dott describes a case of intussusception, and tells Cushing that the techniques that he has learnt from him in Boston have helped him even in his pediatric general surgical practice."¹⁸ By 1925, Dott was an established pediatric surgeon holding an appointment as an honorary surgeon at the Royal Hospital for Sick Children in Edinburgh. He subsequently published articles on hydrocephalus and other pediatric surgical topics, such as anomalies of intestinal rotation. In Edinburgh, Dott was determined "to set up not only his own department of surgical neurology, but also a similar centre of training and influence where precepts he had just learnt could be instilled in young surgeons." That he achieved his aims is well known, yet even "though his credentials were unimpeachable, he never labelled himself 'a paediatric neurosurgeon'."¹⁷ Nevertheless, in 1955 during a major address, he claimed, "Such success as I have had I owe, very largely, to my little patients. I would commend paediatric surgery, as the first training ground in surgical technique and management."¹⁸ Dott

retired in 1962; John F. Shaw, one of his protégés, who had visited Matson in Boston and Bruce Hendrick in Toronto, was "encouraged to take on the paediatric neurosurgical work."

1.2.7 London, England—Hospital for Sick Children

In 1945, Kenneth Till made a favorable impression upon Mr. Wylie McKissock while serving an appointment at Atkinson Morley's Hospital in Wimbledon, England.¹⁹ Till was put "in charge of the smallest ward, the children's ward." As has happened to so many before and after him, a single case experience with a small child suffering from an infected cerebellar dermoid cyst promoted in Till "a decided impetus" to pursue pediatric neurosurgery. Upon completion of his training and his demonstrated preference for working with children, Till nevertheless encountered a negative attitude toward his pursuit of the subspecialty. At the time, the Hospital for Sick Children in London sent patients with neurosurgical conditions to Atkinson Morley's Hospital 15 miles away, where there were no pediatric facilities. Yet, the Hospital for Sick Children was proud of its ability to manage most pediatric conditions and was already a flourishing tertiary referral center. Wylie McKissock, who was on the staff of the Hospital for Sick Children but never actually operated there, was asked to set up a neurosurgical department in that facility; he was apparently not much in favor of the request and demanded resources far beyond the means of most National Health System hospitals. Unexpectedly, his demands were met, and Kevin Till became part of the new team.¹⁹

In the early days of his pediatric practice, Till acknowledged the influence of Ingraham and Matson on his own practice, thereby extending the Boston influence to the United Kingdom. Having spent time in Boston as well as at Children's Memorial Hospital in Chicago, Till was delighted to have Matson journey to London to assist him with the surgical removal of a child's craniopharyngioma.

1.2.8 Mexico City, Mexico—Hospital Infantil de Mexico (F. Rueda-Franco, MD, Written Communication to Dr. Humphreys, May 2004)

The president of Mexico inaugurated the Hospital Infantil de Mexico (Children's Hospital of Mexico) on April 30, 1943. Clemente Robles was the appointed neurosurgeon; however, he acted only as a consultant because there was no special ward for neurologic surgery. As was typical for the time, Professor Robles, a gifted surgeon trained in Europe, operated on the abdomen and within the chest (performing open-heart surgery) in addition to undertaking neurosurgical procedures.

Miguel Ramos-Murguía succeeded Professor Robles in 1953. Returning from the United States, where he trained at the Neurological Institute of New York under J. Lawrence Pool, Ramos-Murguía founded the neurosurgical service at the Children's Hospital of México, the first pediatric neurosurgical unit in the country.

1.2.9 Pacific Rim—Japan, Korea, and Taiwan

Pediatric neurosurgery in the Pacific Rim countries was influenced by North American centers, in particular by Children's Memorial Hospital in Chicago, as noted above. Countries like Japan, Korea, mainland China, and Taiwan also had their neurosurgical giants in the 1930s and 1940s, who provided children with surgical care in situations similar to those existing in Europe and North America at that time.

Yutaka Maki credits Raimondi with initially planting “the first seedling, namely [Satoshi] Matsumoto, in Japan followed by others of his residents, one after another forming a new plantation that would grow into a forest of pediatric neurosurgery.”¹⁹ Matsumoto returned to Japan in 1971, having completed his full residency and research in Bonn, Germany, and “devoted himself to the establishment of [the] Japanese Society for Pediatric Neurosurgery (1973).” Subsequently, other Japanese surgeons interested in pediatric neurosurgery were to travel to Boston, London, Marseille, and Toronto to hone their skills.

Neurosurgery in Korea also began as an offshoot of general surgery (J.-U. Choi, MD, written communication, June 2004). Ventriculo-subgaleal and Torkildsen shunt procedures are listed in the logs of Severance Hospital, Seoul, in the early 1940s. Hun Jae Lee, another pioneer of Korean neurosurgery, who completed his residency training at the University of Michigan under Edgar Kahn in 1957, was allegedly the first to undertake a procedure using the Holter valve in Korea in the late 1960s. However, it is Yoon-Sun Hahn who is credited with initiating pediatric neurosurgery in Korea, following his return home from Children's Memorial Hospital in Chicago.

Subspecialty organizational developments are now apparent in mainland China (where a pediatric neurosurgical society has been formed), as well as in Taiwan (T.-T. Wong, MD, written communication, May 2004). To this day, there continues to be an exchange of interested young men and women who travel worldwide from the Pacific Rim countries in search of supplementary experience in children's neurosurgery.

1.2.10 Paris, France—Hôpital des Enfants Malades

Jacques Rougerie, regarded as the pioneer of pediatric neurosurgery in France in the 1950s, catalyzed discussions about the “individualization” of this discipline with colleagues in Paris.²⁰ His untimely death stalled the deliberations until the mid 1960s, when Jean-François Hirsch “tried to speed up the process.” Hirsch noted that several core issues were examined, the most key being whether children's neurosurgery was to be performed in a pediatric hospital or linked to an adult neurosurgical department in a general hospital. Hirsch clearly preferred the former arrangement. Nevertheless, for Hirsch the process was slow and arduous. In 1970, the first independent service of pediatric neurosurgery in France was established at Hôpital des Enfants Malades in Paris. However, Hirsch claims that it took many meetings to gain an identity for the unit; resources

increased slowly, as did the major alterations to the facilities. In his opinion, it took two decades before the service was functioning at an optimal level.

1.2.11 Philadelphia, Pennsylvania—Children's Hospital of Philadelphia (L. N. Sutton, MD, Written Communication to Dr. Humphreys, January 2004)

The obstacles that surgeons encountered in children's hospitals are illustrated well by the experiences in Philadelphia in the early 1950s. C. Everett Koop (later to become surgeon general of the United States) was instructed by the Chairman of Surgery at the University of Pennsylvania School of Medicine to create a department of pediatric surgery at The Children's Hospital of Philadelphia. Reportedly, Joseph Stokes, then a professor of pediatrics at The Children's Hospital, was reluctant to set up a separate surgical division. Nevertheless, Koop was successful in developing one of the first and largest departments of pediatric surgery in the country. Shortly thereafter, he asked Eugene Spitz to become surgeon in charge of the neurosurgical service, the second such unit dedicated to children in the United States. In 1957, Luis Schut, a resident in neurosurgery at the University of Pennsylvania School of Medicine, was asked to assist Spitz at The Children's Hospital. He then worked with Spitz first as a fellow and later on as an associate. Upon his return in 1962 from Great Britain, where he had obtained experience as a senior registrar, Schut joined Spitz as one of his junior staff members. Schut became known as an important teacher and mentor for scores of residents and fellows at the University of Pennsylvania, many of whom are in the full-time practice of pediatric neurosurgery throughout the world.

1.2.12 Toronto, Canada—The Hospital for Sick Children

Nine years after Kenneth G. McKenzie launched Canadian neurosurgery at the Toronto General Hospital, William S. Keith was appointed in 1933 to the Hospital for Sick Children. In due course, Keith took on the care of children requiring neurosurgical treatment. In preparation, he studied at the University of Chicago and afterward took a clerkship in the neurology service at the National Hospital in London. Upon his return to Toronto, Keith was expected to be equally facile in general and orthopedic surgery, as well as neurosurgery. Keith was not a favorite of the powerful chief of pediatrics, who presided over the hospital as a stern father would over his family. They argued over which patients Keith would operate on and even where he was to park his car.

In 1952, E. Bruce Hendrick, a resident in the postgraduate training program in neurologic surgery at the University of Toronto, was informed that he was being “given the opportunity of a lifetime” to take a year of training at Boston Children's Hospital to study pediatric neurosurgery under Ingraham and Matson. Years later, Hendrick confessed that at the

time “I knew very little about Ingraham or Matson and nothing about pediatrics.”²¹ However, he had observed that despite Bill Keith’s presence, only a few pediatric neurosurgical procedures were being performed at Toronto’s Hospital for Sick Children. As elsewhere, a significant number of children with brain and spinal cord tumors were transferred to the Toronto adult hospital for surgery and then returned to the pediatric service for aftercare and convalescence. Children with head injuries were admitted to the hospital under the care of the general surgeons, who also operated on infants with myelomeningocele. Hendrick thus concluded that pediatric neurosurgery was a minor part of the Toronto neurosurgical scene, as elsewhere. All of that changed after Hendrick returned to Toronto in 1954 to pursue what he described as his “eccentric interests at the Children’s” and to become Canada’s first full-time pediatric neurosurgeon. Hendrick’s later trainees and associates, Robin Humphreys and Harold Hoffman, established a training program in pediatric neurosurgery that became renowned for its excellence and international influence.

1.3 Establishing the Identity of Pediatric Neurosurgery

Surgeons like those just described, who were practicing pediatric neurosurgery around the world, took steps by the mid 1960s to assign identity to their subspecialty. Hirsch reflected that “three pre-requisites [were] to be fulfilled before a specialty can be recognized as such:

1. individualization of a specific body of knowledge;
2. recognition of the specific nature of this knowledge by people who will create the means necessary to the practice and development of the specialty;
3. conferring an official status on it by way of political decisions and the creation of dedicated learned societies.”²⁰

Pediatric neurosurgeons became more and more interested in obtaining new and innovative information about their discipline, and they wanted to participate in forums where they could learn from the experiences of senior or more experienced colleagues.

Specialty organizations were gradually created. The European Society for Pediatric Neurosurgery (ESPN) was founded at the first European Congress of Pediatric Neurosurgery, held in Vienna in 1967; Donald Matson was the guest of honor. In 1972, what was identified then as the American Association of Neurological Surgeons, Pediatric Section, met for the first time in Cincinnati, Ohio; the pediatric section was the first of the subspecialty sections formed within the association. The American Society of Pediatric Neurosurgeons (ASPEN) was formed in 1978. Similar professional organizations have arisen in Japan (1973), Mexico (1999), and most recently Australia (2002). Each is governed by its own bylaws, and each has defined qualifications for membership. The birth of these professional societies reflected the increasing attention to children’s neurosurgery that was taking place around the world and the bonding of their members, who were seeking to develop their skills exclusively for the benefit of children.

In the autumn of 1971, Jacques Rougerie hosted a meeting in Paris, in part to “determine whether this was an opportune time to convert [the ESPN] to an international society.”¹⁶ Some of the individuals identified subsequently as founding members of the International Society for Pediatric Neurosurgery attended that meeting; however, it was concluded that the ESPN would continue as originally intended. Nevertheless, the concept of an international organization had gained momentum, with the result that the International Society for Pediatric Neurosurgery (ISPN) was created in 1972. Its first meeting was hosted by Satoshi Matsumoto in Tokyo in 1973; it was presided over by Jacques Rougerie, President; Anthony Raimondi, Secretary; and Bruce Hendrick, Treasurer.

In 1973, during a pediatric neuroradiology symposium held in Chicago, Illinois, Carrea and Raimondi entered into a discussion about clothing. Raimondi proudly displayed his Colombian *ruana* (or poncho), which was made of plaid wool with a slit for the head. Not to be outdone, Carrea defended the elegant and delicate Argentinean poncho and promised to give one to Raimondi. He did so a year later, and Raimondi protectively tucked it away for “future use.”²² At the request of Raimondi, on Carrea’s death, the poncho became the symbolic vestment of each new president of the ISPN at future meetings. The poncho’s skirts have been embroidered with the names of all the presidents of the society from Jacques Rougerie onward, and it has been passed annually from one president to the next, to impart solemnity and honor to the office.

All of these societies, national and international, devote themselves and their academic endeavors to the research, diagnosis, and care of surgical lesions residing within the child’s nervous system. Specialty-specific journals and multiply authored textbooks dedicated to pediatric neurosurgery have become academic byproducts of these professional bodies.

These organizations have also acknowledged their responsibility for the continuation of specialty education, principles summarized by Concezio Di Rocco in his exhaustive analysis of international education applicable to the specialty.²³ Continuing medical education programs that focus on pediatric neurosurgery have sprung up around the world. Some are topic or technology based, whereas others cover a broad range of issues across the field of endeavor. For example, the education committee of the ISPN organizes academic courses that are held in Third World nations. Meanwhile, in North America, rigorous education and practice standards have been set up for fellowship programs. For several years, the ESPN has conducted triphasic pediatric neurosurgery teaching courses for trainees in Europe.

By the end of the 20th century, pediatric neurosurgery had become an established and recognized subspecialty.

1.3.1 The Establishment of the American Board of Pediatric Neurosurgery and the Formalization of Postgraduate Pediatric Neurosurgical Training in the United States and Canada

As noted previously, the practitioners of pediatric neurosurgery had always demonstrated an unwavering commitment to the

care of pediatric patients and the adequate training of neurosurgeons specializing in the care of children and infants. In the 1980s and early 1990s, it became apparent to many of the leaders in the subspecialty in the United States and Canada that in many North American programs, residents were inadequately trained in pediatric neurosurgery because of limited patient volume and faculty expertise. The majority of established academic and private practice pediatric neurosurgeons agreed that to protect pediatric patients with neurosurgical disorders, standards for the education of pediatric neurosurgeons needed to be established and rigorously supervised. The longstanding question of how one identifies a pediatric neurosurgeon was to be answered by the establishment of an independent board to certify pediatric neurosurgeons based on agreed-upon standards, and to provide a certificate to those individuals who fulfilled the requirements. The goal was nearly accomplished through the standard regulatory channels for the establishment of such credentialing in the United States—namely, a subspecialty certification from the American Council of Graduate Medical Education (ACGME), with the approval of the parent American Board of Neurological Surgery (ABNS). There was great concern among organized neurosurgery, however, that the granting of such a subspecialty certificate would interfere with the clinical practice of neurosurgeons previously certified by the ABNS. Despite the fact that the certification was approved, the mandated requirement of a 2-year period of postgraduate training meant that there were no applications for such certification, and the ACGME and ABNS approval lapsed. Spurred by the knowledge that after many failed attempts to obtain such specialty certification through the usual channels it would never be approved by the current political bodies, a group of prominent American pediatric neurosurgeons, led by David McLone of Chicago, Donald Reigel of Pittsburgh, William Cheek of Houston, and Robert McLaurin of Cincinnati, among others, convened a pivotal meeting at the Chicago O'Hare International Airport in 1996 to define the missions, goals, and structure of the proposed board. They gained a unanimous agreement from the more than 75 pediatric neurosurgeons present to go forward with the creation of what would become the American Board of Pediatric Neurosurgery (ABPNS). This board became the first neurosurgical board to require recertification, and it enumerated requirements for yearly case load and the appropriate pediatric neurosurgical training of diplomates. Concomitantly, the Accreditation Council for Pediatric Neurosurgical Fellowships (ACPNF) was established to regulate and supervise fellowships that were established in North America to train pediatric neurosurgeons, defining the size and composition of faculty, required case volume, composition and quality of the ancillary services at the affiliated pediatric hospitals, and quality of the affiliated residency training programs. In what has been one of the most remarkable aspects of the formation of this independent board and fellowship accrediting body, both the ABPNS and the ACPNF have been widely accepted as the ultimate arbiters in determining the training and qualifications of pediatric neurosurgeons, with the tacit approval of the ABNS to function in parallel with these bodies; the general ac-

ceptance by pediatric hospitals and by academic and private practice centers of the role of the ABPNS and ACPNF in the identification and training of pediatric neurosurgeons was accomplished within 10 years of the founding of the ABPNS.

1.4 Conclusion

The history of pediatric neurosurgery parallels developments in many spheres of surgical practice in the 20th and 21st centuries. At first, the generalist surgeon performed operations on every part of the body; gradually, specialties emerged, and what we now consider expert management of extremely complicated conditions has been fostered by this development. In the past, much time and effort had to be expended to convince hospitals, our colleagues, and our certifying bodies that children are not simply small adults, and that the clinical problems of children are unique and should be treated in unique facilities with unique ancillary services. The individuals over these two centuries who have developed our pediatric neurosurgery subspecialty have been notable for their humanity as well as their clinical and teaching skills, and the present quality of our training and practice remains very much in their debt. It is incumbent on all of us to remember this rich history of pediatric neurosurgery and to recall it to our trainees.

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2 Normal and Abnormal Development of the Nervous System

Timothy M. George and David Cory Adamson

2.1 Introduction

Understanding normal development and the consequences of abnormal early embryogenesis remains vital for the surgeon caring for children with congenital nervous system anomalies. In this chapter, we discuss nervous system defects as they relate to particular embryologic events and the mechanisms causing the malformations. However, a complete description of the development of the human nervous system is a Herculean task beyond the scope of this chapter; therefore, we refer the extensive details of neuroembryology to expert texts^{1,2} and the Web site (http://www.med.unc.edu/embryo_images) for excellent images.

It is always important to bear in mind that the central nervous system (CNS) develops in concert with other organ systems (► Fig. 2.1a). In fact, the development of other organ systems is often instructed by proper CNS development and vice versa. As such, maldevelopment of the CNS is typically coupled to malformations of another organ system (► Fig. 2.1b). From a modern embryologic perspective, the mechanisms causing associated malformations must be studied interdependently. This approach allows an examination of the molecular signaling, tissue interactions, cellular differentiation, and cellular orientation that define organogenesis.

The embryopathy for many defects has not been tested experimentally. We are, therefore, left with many speculative and observational theories to explain the embryogenesis of human malformations. We do not exhaustively review all theories here but give the most recent view on embryopathy based on best experimental data. Only when relevant to the embryology does a broader discussion of multiple theories take place. Secondarily acquired CNS pathology, such as hydrocephalus or syringomyelia, is not discussed.

2.2 Molecular Determinants of Congenital Defects

The evaluation of how molecules effect development and disease can be divided into three categories: genomics, the study of DNA and RNA structure and regulation; proteomics, the study of the control and regulation of protein products within the cell and tissue matrix; and metabolomics, the exploration of pathways metabolites use to govern cellular function. Diseases occur as a disturbance of one or more of these areas. Future diagnostics and treatments will be based on the understanding and manipulation of these molecular substrates.

Congenital defects of the nervous system do not fit into simple genetic syndromes but more often embody complex genetic disorders. For example, many regulatory, structural, and enzymatic genes have been implicated in neural tube defects (NTDs).³ Epidemiologic studies of potential environmental risk factors for NTDs have a relatively long history and have identified several factors (e.g., valproate, maternal diabetes, Agent

Orange) that appear to be related to NTD risk. In contrast, the study of genetic risk factors for NTD has a relative short history. Although traditional approaches to genetic linkage (e.g., LOD [logarithm of the odds] score and affected relative pair analyses) have been applied to the study of other conditions since the 1980s, the data required by such approaches (i.e., DNA from multiple affected individuals within families) are largely unavailable for NTDs.

Insights from the human genome project^{4,5} have suggested that the genome represents a complex biochemical machine functioning in three-dimensional space with three distinct and dynamic interacting parts. DNA coding regions, only 2% of the genome, are responsible for blueprinting protein structure, the repository of heritable traits. “RNA only” coding DNA gives rise to *active* RNAs capable of altering the behavior of normal genes. Consequently, studies designed to identify genes that influence the risk for NTDs did not become feasible until the 1990s, when the Human Genome Project began to provide new information regarding the variability within the human genome. Such advances in our understanding of the human genome have provided new opportunities for studying the genetic contribution to conditions like NTDs (e.g., case-control and family-based genetic association studies of non-Mendelian conditions). Another powerful tool in the identification of genes causing NTDs has been candidate gene studies. Although studies of candidate genes in pathways of folate metabolism and non-folate-related candidate genes also have not yielded any genes or genetic variants that are consistently associated with NTD risk, none of the genes that have been evaluated as NTD risk factors has been studied in sufficient detail to warrant its exclusion as a candidate.

Lastly, epigenetic mechanisms may play a role in NTD causation. Epigenetic regulation of gene expression has been suggested to alter the gene function by several mechanisms; these include methylation of DNA at certain C-C dinucleotide repeat segments, with folic acid acting as a chief donor of methyl groups⁸ enzymatic modification of histone function⁹; and activation or suppression of gene function by transposons,¹⁰ also known as “jumping genes.” Since NTDs have been associated with complex patterns of inheritance and are influenced by environmental agents, it is logical to assume that epigenetic effects and not necessarily mutated gene sequences may be very important in the development of neural malformations.

In addition to direct gene regulation, protein and amino acid structure and function can be directly altered, leading to malformations. Protein sequence, conformation, kinetics, modifications, and interactions can all be implicated in abnormal development. Profiles of several groups of functionally related proteins, including circulatory, cytoskeletal, and stress proteins and other proteins of unknown function, have been demonstrated to be important in the developmental regulation of neural tubes of mice and presumably NTDs.¹¹

In the study of metabolic pathways, metabolomics, folic acid pathways have been implicated to influence the risk for NTDs.¹²

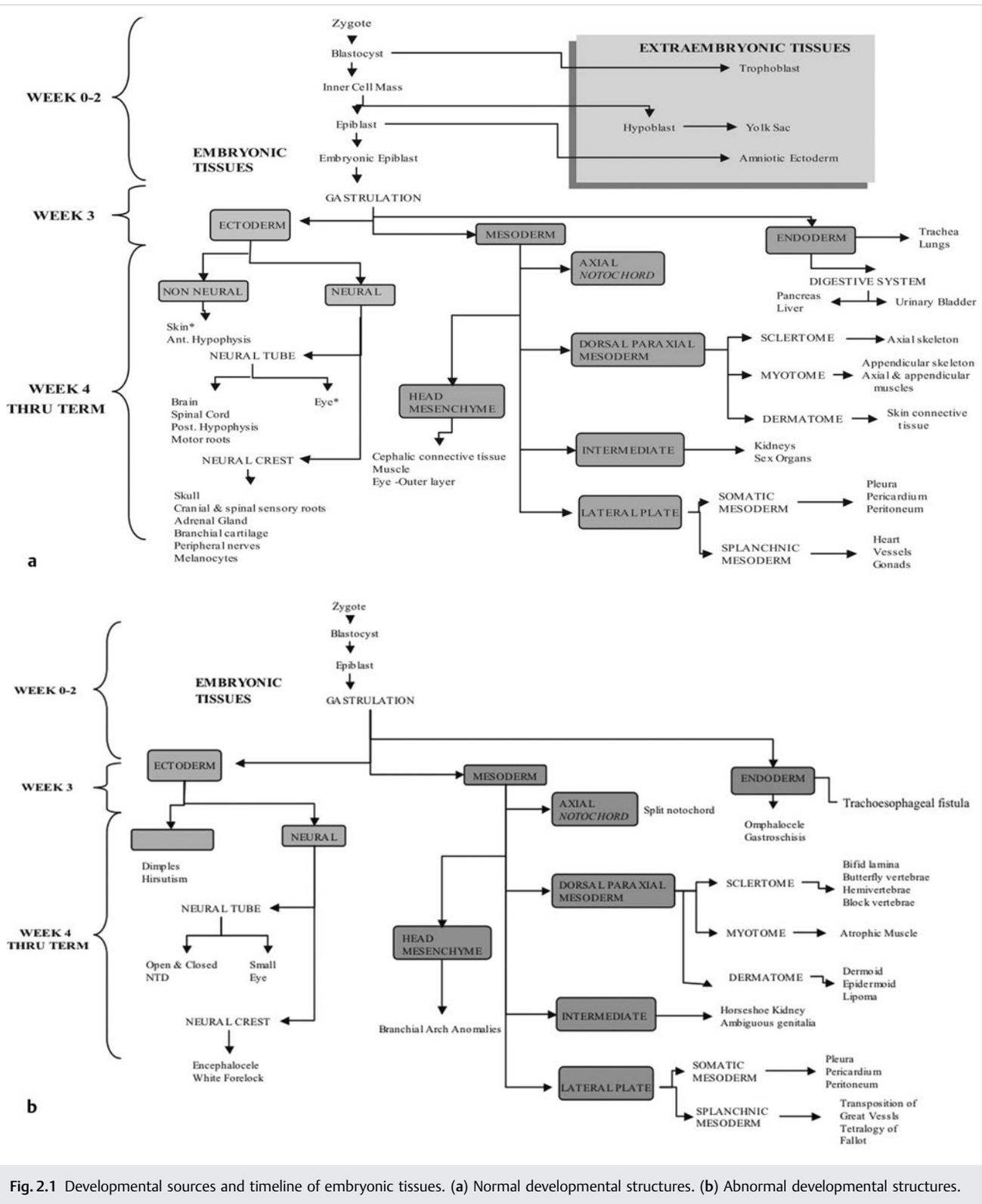


Fig. 2.1 Developmental sources and timeline of embryonic tissues. (a) Normal developmental structures. (b) Abnormal developmental structures.

Studies of mutant enzymes in the folate metabolic pathway, particularly methylenetetrahydrofolate reductase (MTHFR), have suggested a possible association with NTDs.⁷⁻¹¹ The likely role folate plays in the reduction of NTDs resides within the

methylation cycle of homocysteine (► Fig. 2.2). Conversion of homocysteine to methionine occurs when donated methyl groups from folate utilize MTHFR and enzymes that require vitamin B₁₂ as a cofactor. Homocysteine can act as a teratogen

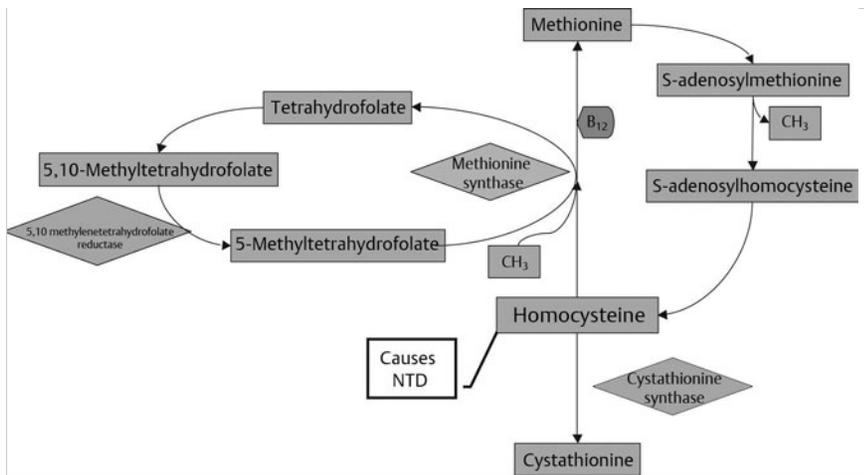


Fig. 2.2 Homocysteine methylation cycle. (Note: Homocysteine perturbs neurulation in experimental animals.) NTD, neural tube defect.

and may be important in human NTDs.^{13–19} The possible association with mutated MTHFR, cystathionine synthase, and altered homocysteine methylation further suggests the importance that folate metabolism may have in human NTDs.²⁰

Currently, whole-genome screening and the bioinformatic processing of genomic data hold the promise of improved molecular analysis of embryologic events. Whole-genome screening has been limited by cost (up to \$10,000 per whole genome), poor understanding of the genome sequence, and the relevance of epigenetic effects. Reduced cost, high-speed genomic sequencing throughput, and better understanding of the genomic and epigenetic impact on disease will change the future of molecular embryology.

2.3 Embryogenesis of the Neuronal System and Malformations

2.3.1 Pregastrulation (Morula and Blastocyst Stages)

During the morula and blastocyst stages, proper cellular orientation or polarity is initially established. By postovulatory day (POD) 5, the embryo has developed from a single fertilized egg, through morulation, and into a 32-cell blastocyst, with an eccentrically placed inner cell mass and a surrounding ring of cells called the trophoblast. The inner cell mass forms the epiblast and the hypoblast, similar to the dorsal (animal) and ventral (vegetal) poles in *Xenopus*.²¹ The epiblast ultimately forms the embryo. These first signs of cell polarity provide the fulcrum for the developing body axis and nervous system induction.

The first obvious feature of rostrocaudal polarity occurs around POD 13, with thickening of the rostral end of the hypoblast into the prechordal plate and the birth of the primitive streak at the opposite end.²¹ The primitive streak elongates cranially in the midline of the embryo and becomes contiguous with the simultaneously developing primitive knot, or Hensen node, at the rostral end. The Hensen node functions as the embryonic “organizer” and is critical to induction of the notochord and neuraxis.

A cascade of factors expressed in a spatially and temporally controlled manner tightly regulates the early steps in the devel-

opment of the body axis. Numerous studies have uncovered several genes implicated in patterning of the primitive body axis; however, the *Wnt1* β -catenin pathway is the most understood.^{22–24} *Wnt1* activates a cascade that increases β -catenin, which directs early expression of target genes, such as *brachyury* and *siamois* (important for proper formation of the primitive streak²⁵), *cripto* (responsible for proper dorsoventral polarity in the epiblast²⁶), and *twin* (required for development of the embryonic organizer²⁷).

In addition, the *Wnt1* β -catenin pathway influences bone morphogenetic proteins (BMPs),^{22–24} which play a significant role throughout neurogenesis but are especially critical during pregastrulation for helping to establish proper rostrocaudal polarity. BMPs subsequently serve as positive inducers of epidermal differentiation during primary neurulation.

Other nonmolecular mechanisms also help to instruct proper axis determination. Proper perpendicular alignment of the embryo with the longitudinal axis of the uterine wall,²⁸ pH and ionic gradients, cell orientation in response to the site of sperm entry into the egg, and/or gravitational forces²² may all affect future embryonic polarity. Clearly, mechanisms governing polarity during pregastrulation are not completely understood; several different processes are most likely involved.

Defects of Pregastrulation

No known malformations occur during the pregastrulation period. Perturbations during these stages would affect the polarity and differentiation of early primordial stem cells, the ability of the embryo to implant properly, and the development of the placenta and critical extraembryonic membranes—all of which would be lethal to the early embryo.

2.3.2 Gastrulation

Establishment of the organizer, primitive streak, and proper embryonic axis marks the beginning of gastrulation, or formation of the three embryonic germ layers (► Fig. 2.3). During gastrulation, a dramatic reorganization of the embryonic cells occurs along the rostrocaudal, dorsoventral, and left–right axes. The initial relationship and orientation of cells established in the blastula are rearranged through coordinated cell move-

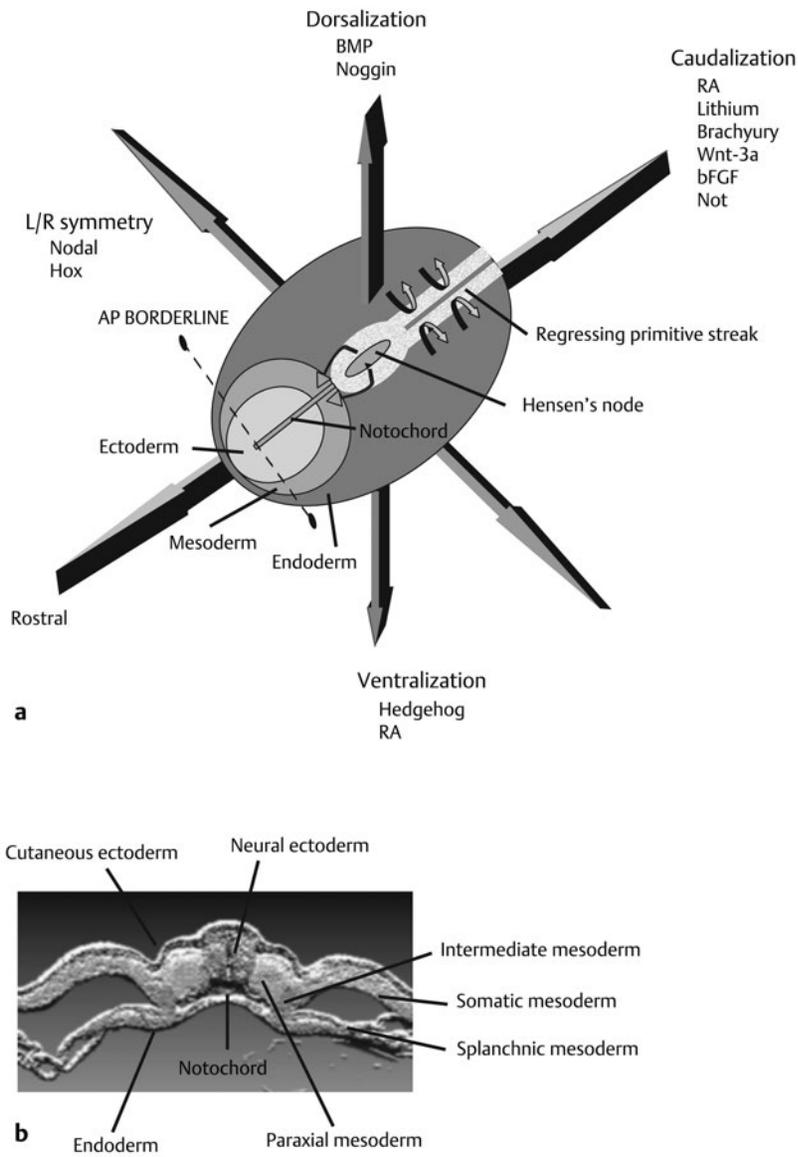


Fig. 2.3 Gastrulation. (a) Schematic of embryonic axis determination. Key is the anteroposterior borderline, which determines the rostral–caudal border. (b) Cross section of a chick embryo demonstrating features of the three embryonic germ layers. AP, anteroposterior; BMP, bone morphogenetic protein; bFGF, basic fibroblast growth factor; L–R, left–right; RA, retinoic acid.

ments. Around POD 16, successive waves of epiblast cells caudal to the Hensen node migrate into the primitive streak and form the prospective endoderm and mesoderm. Epiblast cells immediately around the Hensen node migrate into the node in the midline and then rostrally to form the notochord.

The notochord, located between the ectoderm and endoderm, is vital for determining the rostrocaudal axis of the embryo beginning at the anteroposterior (AP) borderline, thought to occur in the region of the hindbrain–midbrain junction (see ► Fig. 2.3). The notochord also intercalates with the endoderm and contributes to the ventral floor plate region of the future neural tube. Another connection, previously known as the neuenteric canal, occurs in the pit of the Hensen node and connects the ectoderm to the endoderm.²⁹

Several genes have been implicated in these early steps of gastrulation³⁰; however, *brachyury* is clearly required for normal gastrulation movements and development of the three germ layers in embryos.³¹ As cells move away from the streak, *brachyury* expression is downregulated, except in the head

region and notochord. Mice that are homozygously deficient in this gene do not form a primitive streak, have an absent or abnormal notochord, and lack caudal mesodermal structures.³¹ Downstream target genes of *brachyury* must include notochord-forming factors, cell adhesion molecules involved in gastrulation movements, and factors needed to continue expression of *brachyury*.

Dorsoventral patterning is an important event during gastrulation and depends on the proper expression of *brachyury* as well as competitive interactions between ventral signals, such as sonic hedgehog (shh) and HNF- β ,³² and dorsalizing factors from the ectoderm, such as BMP-4, Msx-1, and dorsalin-1.^{33–36} As discussed earlier, the formation of dorsal structures also requires the expression of *Wnt*/ β -catenin factors.³⁷

Establishment of left–right polarity is also thought to occur during gastrulation, with formation of the notochord; however, there is no anatomic correlate. Left–right asymmetry may be related to the asymmetric expression of growth and transcription factors during gastrulation. In avian embryos, activin-bB and its

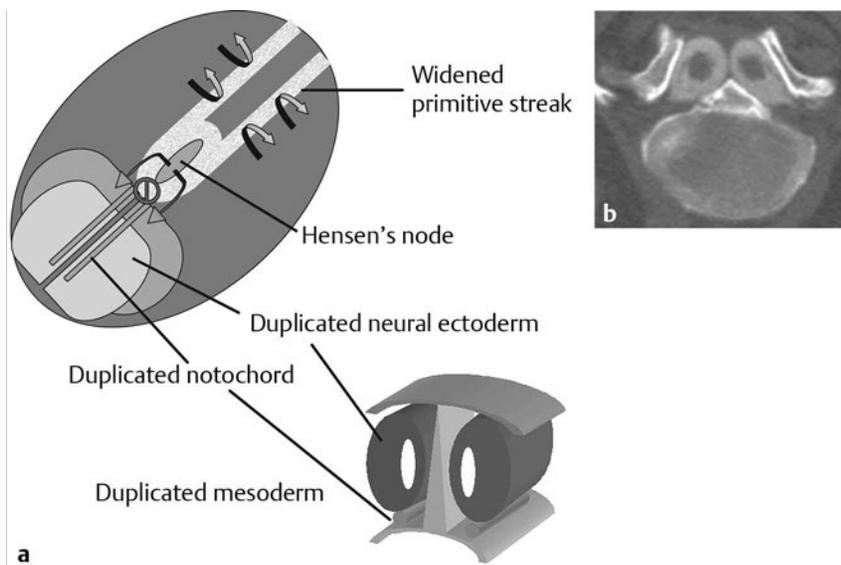


Fig. 2.4 Split-cord malformation. (a) Schematic showing the split notochord and the split ectoderm. (b) Myelogram demonstrating split cord malformation type 1.

receptor are found only on the right side of the Hensen node, whereas *shh* is expressed only on the left. Similarly, in the mouse, *nodal*, a transforming growth factor- β (TGF- β) protein, and *lefty* are found only in the left-lateral mesodermal plate.^{30,38}

Defects of Gastrulation

Defects during gastrulation are thought to affect all three primary cell layers along all embryonic axes. Malformations include split-cord malformations (SCMs); neurenteric, dermoid, and epidermoid cysts; anterior and posterior spina bifida; intestinal malrotations, duplications, and fistulas; anterior meningoceles; and other complex dysraphic malformations. Additionally, congenital tumors, such as teratomas, may have their origin during gastrulation.

Common to this class of defects is the presence of an SCM (► Fig. 2.4). SCM type I, formerly called diastematomyelia, comprises two dystrophic spinal cords separated by a vertical bony bar with two dural tubes. SCM type II, formerly called diplomyelia, comprises two dystrophic cords separated by a fibrous band contained in a single dural tube. Complex SCM, or type III, occurs when one of the dystrophic hemicords forms an open NTD, also called a hemimyelomeningocele. True dimelia, or complete duplication of a normal spinal cord, has not been described.³⁹ These malformations represent a spectrum of defects of a common embryopathic mechanism. The open NTD associated with an SCM further underscores the likelihood that the SCM developed before the NTD.

Many theories exist to explain the embryopathy of SCMs and more complex defects.^{40,41} The common theme is an underlying embryologic defect involving the formation of two notochordal structures. The notochord is split by a retained or accessory neurenteric tract, or it is split by the persistent separation of primitive paired notochordal anlagen. The separation of the notochord induces the formation of two separate neural plates, and retained tissue between the plates forms a tract or rest of pluripotential cells. Laterally displaced somites lead to vertebral anomalies such as butterfly vertebrae. The intervening tissue

contains pluripotential cells capable of developing all three germ layers, including ectodermal malformations (tufts of hair, dermoid and epidermoid cysts); mesodermal malformations (bony, cartilaginous, or fibrous bands; muscle; adipose tissue; vessels); endodermal malformations (intestinal malrotations, neurenteric cysts); and lesions with all three germ layers, such as teratomas.⁴²

The underlying defect remains unknown, but two basic mechanisms are likely: aberrant axial mesodermal cell movements and duplication of normal axial structures secondary to inappropriate instructive signaling. Aberrant cell movements have been described when the Hensen node is surgically split during late gastrulation in chick embryos.⁴³ Inappropriate migration of the notochord has been reported in *brachyury* mutant embryos.³¹ Duplication of the caudal neural tube and notochord is caused by teratogenic levels of exogenous retinoic acid, antisense oligonucleotide inhibition of *engrailed* genes,⁴⁴ or fibroblast growth factor receptor-1 (FGFR-1) manipulation.⁴⁵

2.3.3 Primary Neurulation

Neural Plate Induction, Lengthening, Folding, and Fusion

Primary neurulation is a complex morphogenetic process comprising several independent events that overlap temporally and spatially. The result is the development of the brain and spinal cord down to the S2 level. It can be divided into four major events: neural plate formation, neural plate midline bending, neural plate lateral wall bending, and neural fold fusion (► Fig. 2.5).

The primordial neural plate is first induced around POD 16 as a pseudostratified columnar epithelium.⁴⁶ The process of *induction* occurs when a group of cells establishes, changes, or directs the development of an adjacent group of cells via direct contact or by the secretion of diffusible molecules.⁴⁷ Neural induction is the default of ectoderm differentiation.³⁶ Neuronal differentiation is actively inhibited in the ectoderm by ventral embryonic cells and early ectoderm.³⁶ It appears that BMP-4 is responsible

for neural inhibition and is blocked in the prospective neural ectoderm by antagonizing molecules, such as chordin, noggin, follistatin, and others.^{24,48-53}

The newly induced neural plate is transformed from a flat, oval structure into a narrow, elongated one. Net cell movement is lateral to medial, along with intercalation in the midline to help lengthen the neural plate in the process known as conver-

gent extension⁵⁴ (► Fig. 2.6). Blocking the gene *dishevelled* can disrupt convergent extension.⁵⁵ *T-box* genes similar to *brachyury* as well as *Wnt* pathway factors also appear important for proper convergent extension to occur.^{56,57} Cellular features accounting for transformation of the neural plate are increases in cell elongation and height, cell division, and cell rearrangement or intercalation.

Around POD 17, a shallow midline neural groove in the neural plate forms directly above the notochord, initiating bending of the plate. Induced cells located in the midline of the neural plate change from a spindle shape to a wedge shape, forming a median hinge point (MHP).⁵⁸ Cell wedging during neural plate bending is brought about by the contraction of circumferentially oriented apical microfilaments via a sliding mechanism utilizing actin and myosin,⁵⁹ along with prolongation of the cell cycle.⁶⁰ The notochord-secreted morphogen *shh* is the primary molecular substrate for this phenomenon.⁶¹ Mouse embryos exposed to cholesterol synthesis inhibitors are thought to produce holoprosencephaly and NTDs through an *shh*-mediated mechanism. Additional bending points, dorsolateral hinge points (DLHPs), occur in the cranial and low primitive spinal cord regions of the developing neural tube. The molecular determinants of DLHPs are largely unknown. DLHPs allow the tips of the neural folds to bend inward toward each other and converge.⁵⁸

Neural fold fusion is poorly understood. Cellular mechanisms include interactions of cell surface glycoproteins, interdigitation of cell surface cilia, and formation of intercellular junctions. A surface coat of glycosaminoglycans (GAGs) becomes more concentrated at the fold tips immediately before fusion.⁶² The composition of GAGs changes during neurulation, with hyaluronic acid predominating before fusion and chondroitin sulfate predominating after fusion.⁶² Cell adhesion molecules (CAMs) and cadherin play a role in the separation of the neuroectoderm from the surface ectoderm. As neurulation proceeds, the neural plate stops expressing E-CAM and begins expressing N-CAM and cadherin.

Cilia have become recognized as important in neural tube closure, likely as mediators of neural tube formation and neural fold fusion. It appears that cilia help mediate hedgehog signal transduction pathways.⁶³ *Gli*-type transcription factor activity downstream is controlled by hedgehog and is important for the patterning of cell fate during embryogenesis.⁶⁴ Animal models with mutant cilia developmental genes have disturbed neural

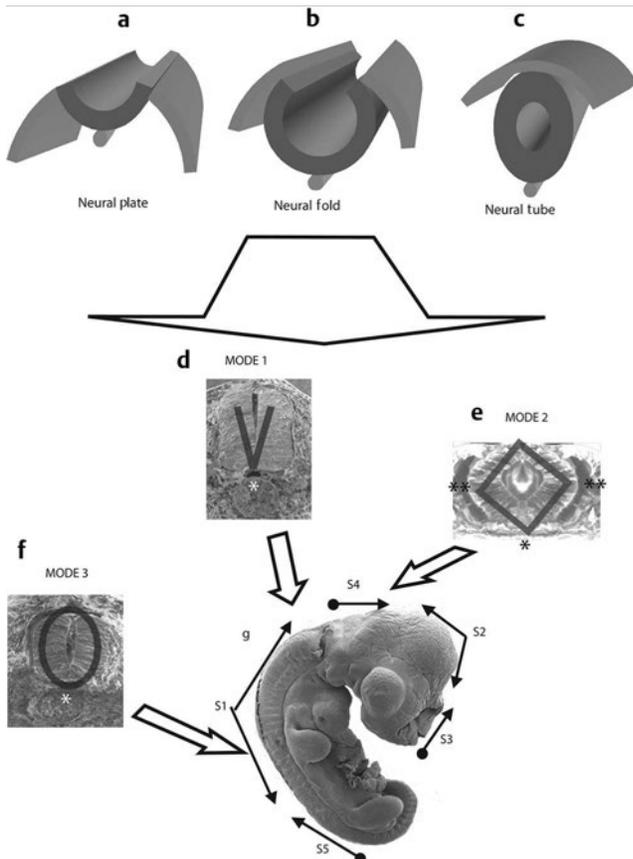


Fig. 2.5 Primary neurulation. (a–c) Neural plate folding, elevation, and fusion. (d–f) Modes of neural tube closure. Mode 1 produces a V-shaped neural tube, mode 2 produces a diamond-shaped neural tube, and mode 3 produces an O-shaped neural tube. (g) Various initiation sites (sites 1 to 5) of neural tube closure.

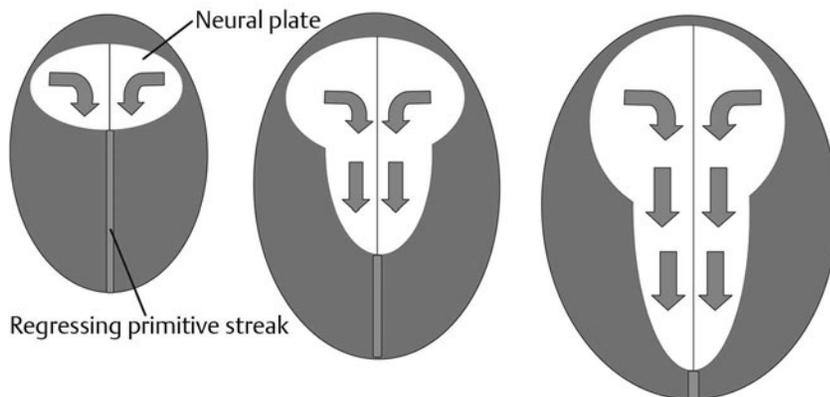


Fig. 2.6 Convergent extension, growth of the neural plate by medial then caudal cell movements.

tube closure.^{65,66} Recently, the *MKS1* and *MKS3* genes have been cloned in the Meckel-Gruber syndrome, which is known to have neural tube defects along with renal and limb abnormalities. The *MKS1* and *MKS3* genes are important in ciliogenesis, implying that cilia are important in neural development.⁶⁷

Toward the completion of fusion, dorsal neural tube cells extend cellular protrusions medially and laterally, bringing about the radial intercalation of deep and superficial cells to form a single cell-layered, pseudostratified neural tube.⁶⁸ Intercellular gaps or tight junction connections are established between cells on apposing neural folds, completing the fusion process.¹ Human neural tube closure occurs between PODs 21 and 28, proceeding from three initiation sites along the neuraxis.⁶⁹ Therefore, the fusion process occurs in multiple discontinuous waves until closure is complete.

Genes such as *PAX3* may be important in neural fold fusion. A paired-type homeobox gene, *PAX3* is expressed in the lateral and posterior neural plate, and expression increases in the dorsal neural tube precisely at the time of neural fold fusion.⁷⁰ Altered *PAX3* function results in NTDs, as seen in the splotch mouse mutant.⁷¹

Extrinsic factors may also contribute to neural tube formation.⁷² These factors include compression of the neural folds by the medial convergence of the surface ectoderm, elevation of the neural folds by the accumulation of underlying mesodermal cells, expansion of the underlying extracellular matrix, and passive buckling of the neural tube by elongation of the notochord and floor plate of the neural tube.⁷³ In addition, newly formed neural crest cells may contribute as they migrate toward the dorsal midline, with two lateral cell groups combining into a single medial population at the roof of the neural tube.⁶⁸

Neural crest cell emigration itself may be a significant determinant of neural tube closure and subsequent dysjunction at the neurocutaneous interface. Neural crest cells are formed from a nidus of cells at the junction of the neural tube and surface ectoderm and migrate laterally after neural tube closure. The *PAX3* and *slug* genes appear to be important in neural crest determination and migration. Human (Waardenburg syndrome)⁷⁴ and mouse (splotch)⁷⁵ mutants of *PAX3* have defects in the migration of neural crest cells. When *slug* is inhibited in chick⁷⁶ or frog,⁷⁷ proper neural crest migration is blocked, and the neural tube fails to close.

Variations in Neurulation along the Rostrocaudal Axis

Neural tube formation is clearly more dynamic and complicated than initially proposed (see ► Fig. 2.5).⁷⁸ At least three different modes of neural tube formation exist throughout the rostrocaudal axis, reflecting different mechanisms. Mode 1 occurs in the cervicothoracic region, where a distinct MHP forms without any evidence of DLHPs. The neural folds remain straight, resulting in an ovoid tube and slit-shaped canal. In the midbrain-hindbrain region, mode 2 occurs, with the appearance of a MHP and DLHPs. After fusion, the tube takes on a diamond-shape configuration, foreshadowing the shape of the fourth ventricle. Neural tube formation in the lumbosacral region, mode 3, involves only a suggestion of DLHP formation in addition to the well-developed MHP, forming a more circularly shaped tube

with a large, patent canal. These neural tube differences may account for some regionally specific abnormalities.

Before the neural tube completely closes, the cranial portion begins to undergo rapid expansion due to increased growth of the tube and enlargement of the ventricular system.⁵² Closure of the cranial neuropore with spinal canal occlusion isolates the ventricular system and increases the intraventricular pressure, which may drive brain enlargement.⁴⁹

The anterior neuropore closes at about POD 24 as a thickening in the dorsal portion of the embryonic lamina terminalis, the future site of the anterior commissure.⁷¹ The caudal neuropore closes at about POD 26,⁴⁹ corresponding to vertebral level S2. It appears that in humans, most of the spinal cord, as far as the S2 level, forms by primary neurulation; the filum terminale and lower sacral levels form by secondary neurulation.

After neurulation is completed, the neural tube is clearly segmented along the AP axis into the various components of the future CNS. An important landmark in nervous system segmentation is the AP borderline that resides in the midbrain-hindbrain junction.⁷⁹ Segmentation is not a function of neurulation but is determined earlier in development by the rostrocaudal gradients of homeotic gene expression. These gradients set in motion the sequential expression of sets of embryonic gap genes, pair rule genes, and segment polarity genes, each set resulting in progressively greater segmentation.⁸⁰

Defects of the Primary Neural Tube (Anencephaly, Cranioraschisis, Myelomeningocele, Myeloschisis)

Open human NTDs (► Fig. 2.7) include the common nonsyndromic anencephaly, cranioraschisis, myelomeningocele, and myeloschisis and reflect a spectrum of defects that occur during primary neurulation. Infants with anencephaly or cranioraschisis do not survive; therefore, these conditions are clinically irrelevant. However, it is imperative that these lesions be understood to discern how the clinically important myelomeningocele and myeloschisis develop. Four developmental mechanisms for open NTDs have been proposed based on data from humans and laboratory animal models: (1) factors important to intrinsic patterning to the neural plate, (2) factors extrinsic to the neural plate, (3) factors important along the rostrocaudal embryonic axis, and (4) reopening of a closed neural tube.

The first concept proposes that open NTDs are the result of an abnormality directly within the neuroepithelium. Studies of patterning and induction of the neural plate have revealed that ventral and dorsal neural plate structures are developed by specific but independent signaling cascades,^{81,82} and they are considered separately in the following paragraphs.

The essential ventral cellular element for neural tube closure is the MHP. Ventral signaling molecules, such as *shh*⁸³ and *HNF-β*,⁸⁴ specify the formation of wedge-shaped cells required for neural plate folding. The phenotype of cranioraschisis in mutant animals, in which the neural tube is open from the level of the midbrain to the lower spinal levels, is thought to be the result of abnormal MHP determination. The telencephalon and midbrain close normally, indicating that the dorsal elements that lead to fusion are normal. In the four mouse mutants with cranioraschisis, *dishevelled*,⁸⁵ *loop-tail*,⁸⁶ *circletail*,⁸⁷ and *crash*,⁸⁸ the neural folds elevate normally but are widely spaced at the

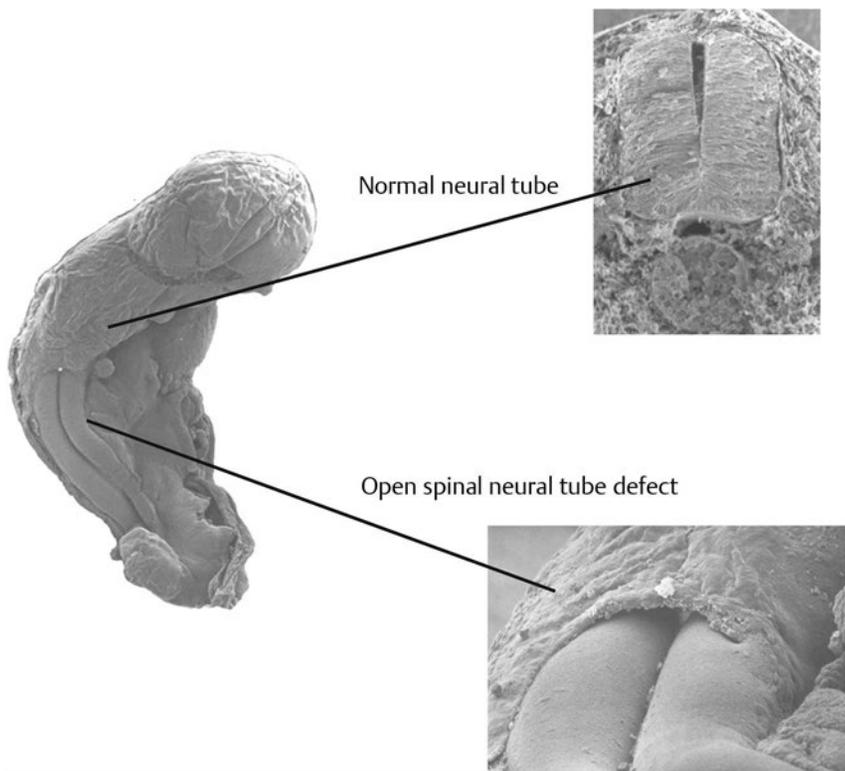


Fig. 2.7 Open spinal neural tube defect. Note how the medial hinge region is normal and cutaneous ectoderm remains attached at the lateral borders of the neural plate.

initial closure site. At the cellular level, abnormal neural plate development in cranioraschisis resulted from disturbed convergent extension, a consequence of disturbed *Wnt* signaling pathways.⁵⁵ Disturbed convergent extension yields a shortened and broad neural plate, and thus a widened and misshapen MHP. The relevance of this model is that neurulation in the hindbrain and upper spinal cord depends on proper MHP development, and any abnormality affecting MHP development is likely to be lethal in humans.

Critical dorsal neural plate determinates for neural tube closure are the proper formation of the DLHPs and the fate of roof plate precursors. Animal models with dorsal neural plate abnormalities have cranial defects, lower spinal defects, or a combination. The key mouse mutant for this model is the *splotch-PAX3* mutant.⁷⁵ In humans, *PAX3* is defective in patients with Waardenburg syndrome, with a subset having spinal NTDs.⁷⁴ The *PAX3* gene is expressed in the presumptive dorsal neural plate, neural crest, and paraxial mesoderm that gives rise to skeletal muscles.⁸⁹ In the *splotch* mouse, the MHP is normal, but the DLHP region is not. This has been confirmed in chick embryos treated with antisense oligonucleotides to *PAX3*.⁷¹ It is not known how mutant *PAX3* causes NTDs; increased apoptosis,⁹⁰ faulty pyrimidine synthesis, or alterations in cell migration^{91,92} have been proposed.

In addition, altered function in neural crest precursors of the presumptive roof plate may alter neural tube closure. *Splotch* demonstrates repressed neural crest migration activity. Chick embryos treated with antisense oligonucleotides to *PAX3*⁷¹ or *slug*,^{76,93} important in neural crest precursor migration, demonstrate open spinal NTDs.

The second concept proposes that properties extrinsic to the neural tube are responsible for open NTDs. The best model is the

curly tail mouse, which develops a lumbosacral myelomeningocele and is a phenocopy of nonsyndromic NTDs in humans.⁹⁴ The inheritance, genetics, and response to periconceptual vitamins make this an attractive model for human caudal NTDs. At the tissue level, mutant curly tail embryos exhibit a cell type-specific abnormality of cell proliferation that affects the gut endoderm and notochord, and not the neuroepithelium.⁹⁵ The reduced rate of ventral embryonic cell proliferation results in a growth imbalance between ventral gut primordia and dorsal neural elements. The result is a delay in posterior neuropore closure because of abnormal caudal flexion, resulting in spinal NTDs.⁹⁶

The third concept is based on the location of the NTD as determined by rostrocaudal patterning. One common theme when the location of the defects appears to respect the restricted gene expression along AP axis domains established during gastrulation. The establishment of an AP borderline determines mesodermal and ectodermal tissue specification and gene expression. This transition zone exists between the midbrain–hindbrain boundary and is defined by rostral expression of *otx* genes and caudal expression by *engrailed* and *hox* genes.⁷⁹ At the tissue level, the variation of gene expression along the rostrocaudal axis mirrors the variation in mechanisms of neural fold elevation, folding, and fusion (see ► Fig. 2.5). According to the model proposed by Shum and Copp,⁷⁸ regional rostrocaudal differences in modes of neural tube closure will cause different types of open defects. Defective mode 1 causes cranioraschisis by interfering with MHP formation. Defects of mode 2 cause exencephaly due to defective DLHP function. Mode 3 defects cause open spinal NTDs.

Additionally, many mutant mouse models have demonstrated that the number and location of the NTDs can vary along the neuraxis. For example, *patch*, *PAX3*, and *short-tail*

mutants have defects localized caudal to the AP borderline, whereas *apoB*, *hox-a1*, and extra-toes mutants have defects rostral to the AP borderline. Several mutants with craniorachisis have defects spanning the entire neuraxis.

The last mechanism proposes that a properly neurulated neural tube can be reopened. The only spontaneous mutant in which this mechanism occurs is the curtailed mouse, in which increased cerebrospinal fluid pressure is thought to rupture a thinned roof plate and dermis in the absence of competent dorsal bony vertebrae.⁹⁷ Although the curtailed mutant may indeed have a reopening of a previously closed neural tube, this mechanism seems unlikely in human NTDs.

However, the reopening model is relevant for the neurosurgeon because the animal experiments that formed the basis for fetal repair of the myelomeningocele were predicated on a surgically generated “reopening” model.⁹⁸ In the animal models tested, repair prevented intrauterine injury from either the toxic effects of amniotic fluid or direct intrauterine trauma.⁹⁹ Regardless, no clear correlation can be made between the structural defect in these animal models and what occurs naturally in human myelomeningocele.

The Myelomeningocele Placode

Understanding the embryology of the myelomeningocele placode is of vital importance when novel repair strategies like intrauterine closure and spinal cord regeneration are considered. The placode has been described as a partially functional or nonfunctional remnant of the unneurulated spinal cord, and little is known about the cellular patterning or connectivity within the placode. The placode has preserved dorsal and ventral cord elements—for example, nerve roots and ganglia—but the exposed neural tissue demonstrates hemorrhages and abrasions indicative of injury.¹⁰⁰ The placode exhibits abnormal cellular patterning along the dorsoventral and rostrocaudal axes, indicative of a change in pattern determination with a paucity of maturing neurons.¹⁰¹ Surgical repair will be predicated upon uncovering the true nature of the structure and function of the neural placode.

Other Defects of the Primary Neural Tube (Meningoceles)

Malformations like meningoceles, cervicothoracic meningoceles and myelomeningoceles, and meningocele manqué are completely or partially skin-covered and are not generally grouped with open defects.¹⁰² However, these lesions should be considered defects of primary neurulation. There is often evidence of limited dorsal myeloschisis in which the dorsal neural tube fails to fuse but neurocutaneous dysjunction occurs normally. Patients usually have normal neurologic function; therefore, it has been presumed that the patterning of the spinal cord is also normal. The molecular, cellular, and tissue-specific mechanisms for the development of these malformations are not known.

Defects Involving the Dorsal Ectoderm (Dermal Sinuses, Dermoid Cysts, Epidermoid Cysts)

Dermal sinuses and dermoid and epidermoid cysts can involve any level of the neuraxis, from the most rostral cranium to the

caudal sacrum. Dermoid cysts include elements of mesoderm and ectoderm (skin, hair, sweat glands, and sebaceous glands), whereas epidermoid cysts are composed only of ectodermal elements (squamous epithelium). Dermal sinuses can be associated with tufts of hair. Whether or not to include coccygeal dimples in the spectrum of dermal sinuses is unclear. It is not clear if these are the remnant of the regressed primitive pit or a forme fruste of a dermal sinus overlying the caudal part of the spine. Since dermal sinuses can be associated with SCMs and completely neurulated CNS structures, it remains unclear if these are disorders of gastrulation or late primary neurulation.

The most discussed mechanism involves incomplete dysjunction of the neurepithelium from the cutaneous dorsal ectoderm (► Fig. 2.8). It is thought that incomplete dysjunction occurs at one of the closure sites of the neural tube. There remains a persistent attachment between the neurepithelium and surface ectoderm. What governs dysjunction of the surface ectoderm from the neuroectoderm after neural tube closure is not completely known, but several possibilities exist, as previously discussed.

2.3.4 Secondary Neurulation

Secondary neurulation is less understood than primary neurulation and begins at POD 25 to 27. The secondary neural tube continues as an extension of the primary neural tube as it grows caudally from the region of the posterior neuropore. It is important to view secondary neurulation as part of the sequence of events in the development of the embryonic tail. Therefore, mechanisms that determine mesodermal and neural elements are intimately linked together.

In mammals and birds, the secondary neural tube arises from cavitation, not from folding of the neural plate as at more rostral levels. Descriptively, the process of cavitation involves the development of a central core of cells called the medullary cord. The outer cells of the medullary cord elongate and become radially arranged columnar cells, probably as a consequence of microtubule changes. A central core of haphazardly organized cells undergoes apoptosis, accounting for much of the cell loss and lumen formation during secondary neurulation.

Fate mapping studies have suggested that rostrocaudal organization may represent a continuous program between primary and secondary neurulation, and that it functions in concert with caudal regression of the primitive streak and mesodermal precursors (► Fig. 2.9). Instead of the classic description of mesenchymal to epithelial transformation, it appears that secondary neural tube cells migrate in stereotyped predetermined pathways from rostral proneural structures.¹⁰³ Therefore, primary neurulation and secondary neurulation appear to involve similar morphogenetic movements; however, in contrast to what occurs in primary neurulation, extensive bilateral cell mixing is observed on the dorsal side in secondary neurulation.¹⁰⁴ The cell movements of the secondary neural tube resemble the movements of convergent extension and may be regulated by *PAX3–Wnt* interactions.¹⁰⁵

Beginning around POD 43 to 48 and continuing through early postnatal life, the caudal neural tube undergoes morphogenetic changes leading to conus medullaris ascension.² This occurs by retrogressive differentiation, in which the caudal neural tube loses much of its diameter and fails to develop a distinct mantle

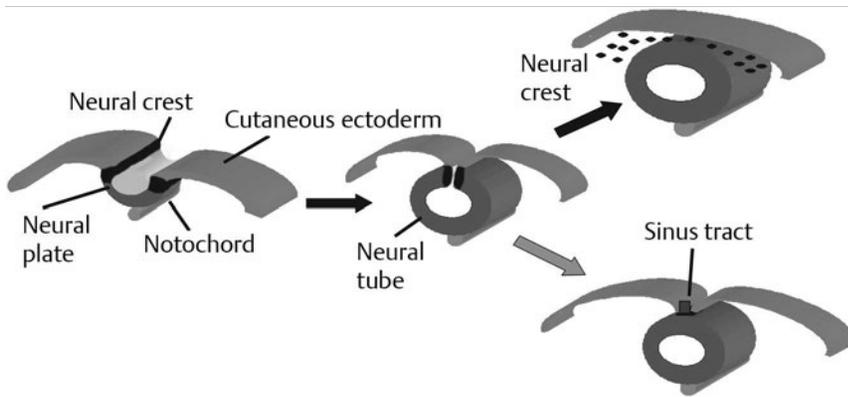


Fig. 2.8 Sinus tract formation; schematic of incomplete dysjunction of ectoderm after neural tube closure.

zone, as well as differential growth of the spinal cord and adjacent vertebral column.² The final position of the conus medullaris is between vertebral levels T12 and L1–L2.¹⁰⁶

Genetic mechanisms for secondary neurulation are still largely unknown. Mutant mice have shown that *brachyury* and components of the *Wnt* signaling pathway control cellular migration and the promotion of mesoderm formation in the caudal embryo. Midkine, a growth factor with neurotropic activity, is one of the few proteins implicated in secondary neurulation.¹⁰⁷ *Brachyury*, *Wnt*, and midkine are thought to regulate secondary neural tube formation by affecting caudal inducing signals. Altered *PAX3* expression may play a role in secondary neural tube by affecting neural crest migration or by maintaining inductive-signaling competence in the neural plate.¹⁰⁸ In addition to the above factors, retinoids have been demonstrated to influence caudal cell movements.^{79,105} In humans, mutation in the *HLXB9* transcription factor causes an autosomal-dominant form of sacral agenesis and may be important in the caudal migratory process of mesodermal precursors. Instructive caudal signals and responsive caudal neural plate elements are needed for proper secondary neural tube formation.

Defects of the Secondary Neural Tube (Abnormal Filum Terminale, Terminal Lipoma, Myelocystocele)

Secondary neural tube anomalies can occur independently or be associated with malformations of primary neurulation, gastrulation, or the caudal cell mass or with mesodermal malformations. Impairment in proper stereotyped morphogenic movements of the caudal neural plate and regressing primitive streak likely accounts for anomalies of the filum terminale and conus medullaris (see ► Fig. 2.9). Pathologically, an abnormal filum can be composed of adipose, fibrous, nervous, or muscle tissues that are derived from secondary neural tube and primitive streak mesodermal precursors.^{109,110} The abnormal tissue is located closer to the conus medullaris because it fails to migrate away to its proper position.¹¹¹

Whereas abnormalities of the filum appear to result from impaired migration, it is likely that the myelocystocele results from improper differentiation and cell fate determination of axial caudal structures. The myelocystocele consists of a dilatation of the caudal central canal of the spinal cord into a glia- and

ependyma-lined cyst surrounded by an expanded terminal spinal cord with an associated lipoma. The terminal dural sleeve is also dilated, producing a double saccular structure. The frequent association of the myelocystocele with other caudal malformations—for example, as part of the VATER (vertebral anomalies, imperforate anus, tracheoesophageal fistula, renal anomalies) or OEIS (omphalocele, cloacal exstrophy, imperforate anus, spinal anomaly) complex—further suggests that this malformation is induced at a time when the fate of the caudal cell mass and terminal spinal cord is being determined.

Defects Involving Dorsal Mesoderm (Spinal Lipomas)

Spinal lipomas include the intraspinal lipoma and lipomyelomeningocele. The intraspinal lipoma lies within the dural sac and typically involves the lumbosacral spinal cord. In the lipomyelomeningocele, the lipoma intercalates into the dorsal spinal cord but additionally extends through a meningeal defect, bifid lamina, and lumbodorsal fascial defect to rest in the subcutaneous tissue. The lipomyelomeningocele is believed to arise during primary neurulation, but the exact timing is not clear. Naidich et al¹¹² proposed the theory of premature dysjunction leading to this defect (► Fig. 2.10). The cutaneous ectoderm prematurely separates from the neuroepithelium, allowing the incarceration of undifferentiated mesenchyme that would normally form meninges or fibroblasts. Key mysteries in these disorders include the source of the adipose cells and how these cells ingress into the developing spinal cord.

One problem with the theory of premature dysjunction is that the surface ectoderm is attached to the dorsal third of the closing neural tube. Once the neural folds come into apposition, the surface ectoderm separates from the neuroepithelium to permit final fusion into the neural tube. This implies that for premature dysjunction to occur, the surface ectoderm has to begin to separate very early in neural fold elevation and folding. Early separation may affect external forces needed for closure of the primary neural tube and result in an unneurulated spinal cord.^{38,61} Dorsal signals from ectoderm important in dorsal neural tube development, such as BMPs, would probably be abnormal if the ectodermal–neuroepithelial interaction was disturbed. Abnormal dorsal signaling would result in more widespread abnormalities in the dorsal neural tube than are seen in typical malformations.

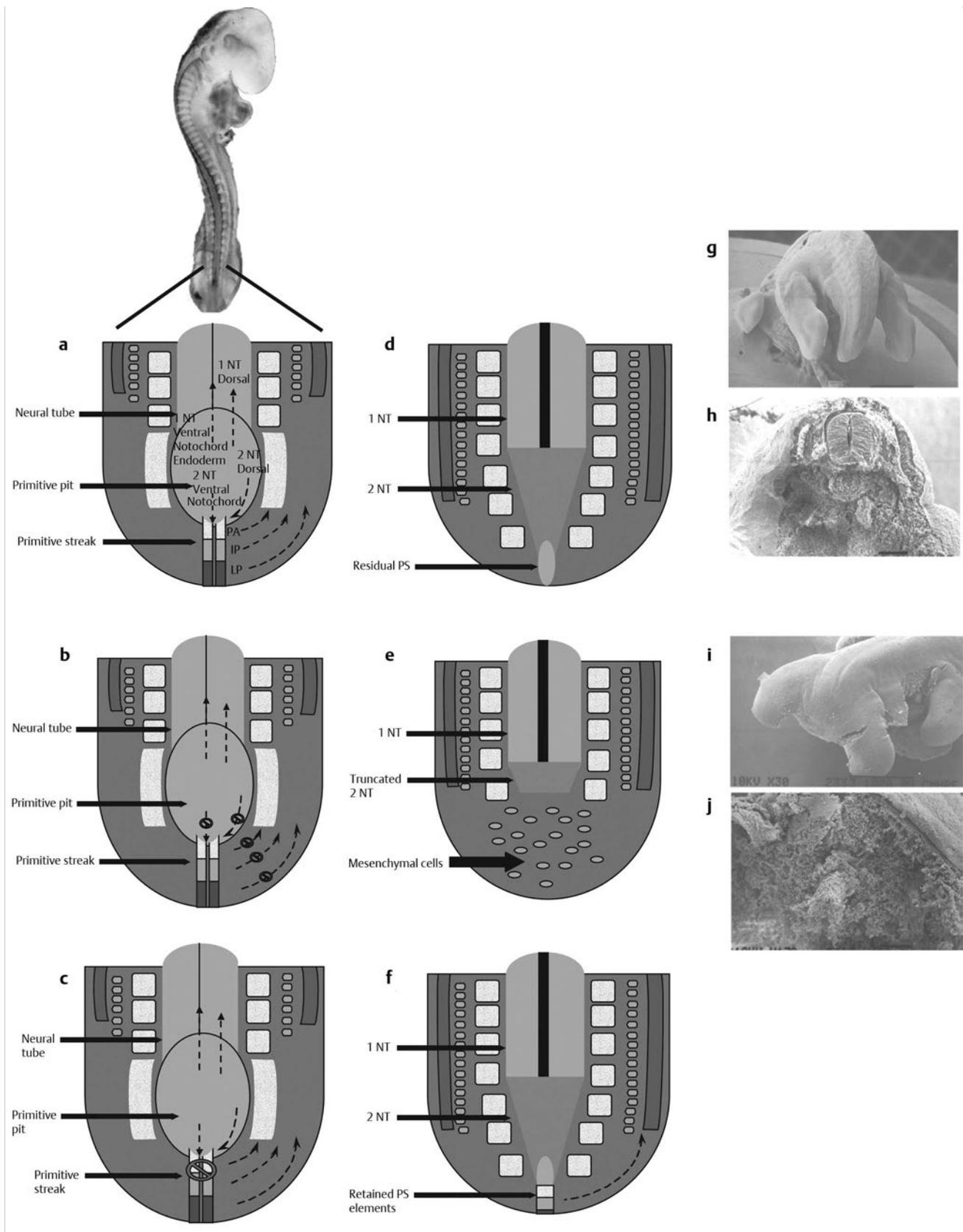


Fig. 2.9 Secondary neurulation, cell movements, secondary neural tube, and tail defects. NT, neural tube; PS, primitive streak.

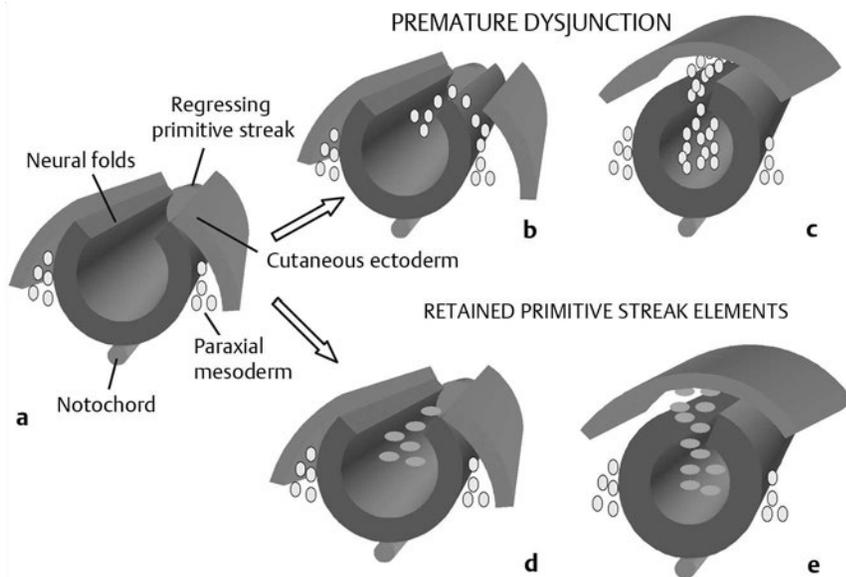


Fig. 2.10 (a–e) Mechanisms of spinal lipoma formation. (b,c) Paraxial mesoderm migrates into the neural tube after the ectoderm separates prematurely. (d,e) Retained caudal primitive streak elements fail to migrate and are retained in the neurulating spinal cord.

Contrary to what was previously thought, adipocytes typically do not arise from meninges, vessels, or glial cells, and spina bifida cannot be explained by the incarceration of mesodermal tissues during primary neurulation or developmental defects at the level of the tail bud.¹¹³ Although adipocytes can be derived from fibroblasts,¹¹⁴ multiple problems exist with this theory based on current data on cell fates. At the stage when the neural tube is closing and premature dysjunction would occur, the fate of the mesenchymal cells comprising the paraxial mesodermal anlage has not yet been determined. This implies that if a lesion did develop, it should be composed of elements derived from this paraxial mesoderm (dermatome, myotome, sclerotome) instead of only adipocytes or fibroblasts.

It has been demonstrated that the dorsal paraxial mesodermal differentiation responds to specific inducers of cell fate (► Fig. 2.11). The dorsal neural tube, ectoderm, and lateral plate mesoderm induce the somite to differentiate into the dermatome and myotome, likely from mesodermal signaling molecules such as *Wnt* and BMPs. The ventromedial region of the somite is induced by ventralizing signals, such as *shh*, from the notochord and ventral neural tube to form sclerotome. Neither *Wnt*¹¹⁵ nor *shh*¹¹⁶ induces adipocytes, but BMP-2 has been shown to induce adipocytes under the proper permissive conditions.¹¹⁷ Therefore, for the dorsal mesodermal anlage to become adipocytes, an inducing signal such as BMP-2, a responsive mesoderm, and/or a factor that prevents normal differentiation would have to be present.

Another mechanism is that mesenchyme from regressing primitive streak becomes retained within the lumen of the folding caudal neural tube by failing to migrate to a specified caudal position (see ► Fig. 2.10). This mechanism does not require abnormal dysjunction. Instead, the retained cells inhibit proper neurulation and meningeal, dorsal vertebral, and paraspinous muscle midline fusion. These cells are destined for a mesoder-

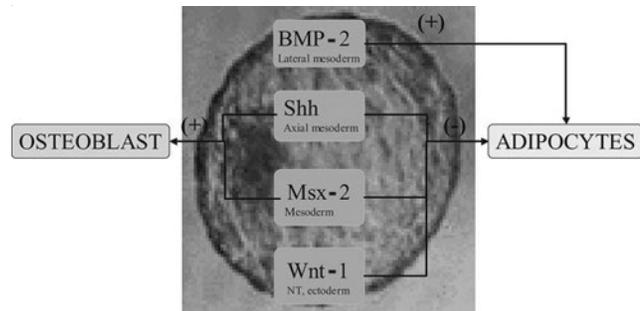


Fig. 2.11 Genes that regulate mesoderm differentiation into adipocytes. NT, neural tube.

mal fate and would then lose caudal repressive *Wnt* signals and respond to lateral mesodermal signals that induce an adipocytic fate. Additionally, retained mesoderm occurs with an improperly migrated primitive streak that leads to the frequently associated abnormalities of the filum.

Defects Involving the Caudal Cell Mass/ Primitive Streak (Caudal Agenesis, Caudal Regression, Sacral Agenesis)

Caudal agenesis, sacral agenesis, and caudal regression syndrome are synonymous terms that describe nonsyndromic malformations ranging from partial to complete absence of the coccyx and sacrum or of the spine up to the lower thoracic vertebrae. Although four patterns of caudal agenesis have been described, two variants of caudal agenesis are most relevant to neurosurgeons: type I, a truncated and high conus medullaris, and type II, a tethered and low conus medullaris that may require a

tethered cord release. All forms of caudal agenesis represent variations of the same mechanism and consist of malformations encompassing all three germ layers (see ► Fig. 2.9). The association of caudal agenesis with the genetic malformation syndromes VATER and OEIS further implicates involvement of all three germ layers. Caudal agenesis is often associated with anomalies of secondary neural tube development, such as lipomas of the filum terminale.¹¹⁸⁻¹²⁰

The caudalmost part of the embryo is still undergoing gastrulation as the primitive streak regresses during tailbud anlage stages of development. The main developmental defect in these malformations is failure or interruption of caudal regression of the primitive streak. Failure of proper migration of cells from the primitive streak produces a shortened embryo and rumplessness in experimental chick embryos.

Disturbance of secondary neurulation, seen as a truncated conus medullaris, is commonly associated with caudal agenesis. It can be presumed that the permissive environment for the continuation of caudal cell movements involved in secondary neurulation is arrested during improper primitive streak regression. Direct evidence for inductive signals for the secondary neural tube has not been described; however, faulty notochord and caudal cell mass development is associated with partial or complete secondary neural tube formation in several mutants. In humans, this phenomenon is seen in sacral agenesis in association with an abnormal T-locus (*brachyury*).¹²¹

Embryology of the Tethered Cord

Tethered spinal cord is a clinical syndrome in which traction on the spinal cord leads to functional deterioration.¹²² Spinal dysraphisms are the source of tethering in this syndrome. Traction leads to stretching of the spinal neurons and microvascular ischemia, resulting in neuronal dysfunction. What makes the spinal cord susceptible to the effects of traction remains poorly understood. In dysraphic defects, it is clear that the spinal cord has significant patterning abnormalities. Developmental data suggest that abnormalities in secondary neurulation result from improper caudal cell migration.¹⁰³ This implies that the distal conus also may be abnormal.¹²³ Examination of the distal spinal cord and tethered filum demonstrates changes suggesting that the distal cord may be abnormal along with the filum.¹¹⁰ Conus and distal spinal cord abnormalities may make these structures susceptible to the forces transmitted by the tethered filum.

2.3.5 Postneurulation Development

Neural Crest

The ectoderm-derived neural crest cells begin to appear around POD 20 in the mesencephalic and rhombencephalic regions and continue to appear along the more caudal neuraxis until POD 32.³² These cells migrate laterally in a dorsal or ventral pathway, and they eventually differentiate into a variety of markedly dissimilar cell types. A cranial neural crest cell population gives rise to the craniofacial mesenchyme (cartilage, bone, cranial

neurons, glia, and connective tissues of the face), thymus, tooth primordium, inner ear cartilage, jaw, primary meninx that forms pia and arachnoid, cranial Schwann cells and melanocytes, cranial nerve ganglia, optic primordium, and optic sheath.^{29,124,125} Truncal and sacral cell populations migrate laterally to form truncal melanocytes, peripheral nerve Schwann cells, primary meninx of the spinal cord, dorsal root and autonomic ganglia, and the adrenal medulla.¹²⁶ Factors involved in the migration and terminal differentiation of these pluripotent cells have been extensively reviewed.¹²⁷

Axial Skeleton

The vertebrae develop from the sclerotome, mesenchymal cell populations derived from ventral somites. The somites themselves are segmentally repeating cell populations of paraxial mesoderm. Somite formation appears to be largely driven by *hox* gene expression, similar to the *hox*-driven segmentation and development of the neural tube. Disruption of the gene pathways necessary for establishing somite divisions results in perturbed somite and vertebral column segmentation; however, the somites that do form will continue to develop into regionally specific sclerotomes and dermamyotomes.¹³²

Sclerotome cells that contribute to the vertebral column migrate to surround the axial midline neural tube, condense, and differentiate into chondrocytes, forming a cartilaginous skeletal framework that is later replaced by bone. The notochord is essential not only for future neuraxial development but also for induction of the sclerotomes and subsequent differentiation of the cartilage forming the vertebral bodies and intervertebral disks. These functions of the notochord appear to be mediated by *shh*.¹³³ Additionally, the products of *pax1* and *MFh1*, expressed in the developing sclerotome, are required for proper vertebral column development. Embryos lacking these gene products lack structures dorsomedial to the vertebral column, develop spina bifida and myelomeningoceles, and have missing vertebral bodies and disks.¹³⁴

The basiocciput develops from mesodermal contributions limited to the occipital and otic regions of somite mesoderm.¹³⁵ Genes, such as *pax1*, have been found to be particularly important at the cervico-occipital transitional zone at the first five somites.¹³⁶⁻¹³⁸ The *pax1* gene is strongly expressed in the region surrounding the notochord and remains until the cartilaginous anlage of the basioccipital bone has developed.¹³⁹ The fusion of the dens axis with the body of the axis also coincides with switching off of the *pax1* gene.¹³⁹ Anomalies of basiocciput segmentation and fusion may account for a small posterior fossa and Chiari malformations.

Postneurulation Defects

Encephaloceles

An encephalocele is a skin-covered herniation of fairly well-organized brain tissue through a defect in the skull. Microcephaly is common, and hydrocephalus can occur but is likely a

consequence of the defect rather than a cause. It is generally believed that the defect occurs during the postneurulation period of rapid brain growth. Therefore, these lesions should not be classified as NTDs. Impairment in chondrocranial growth from an impairment of mesenchyme allows the brain to herniate in animal models.¹⁴⁰ Encephaloceles have been described in the forebrain overgrowth mouse mutant and localized to chromosome 10, but the gene has not been sequenced.¹⁴¹ Multiple teratogens and environmental factors have also been implicated.^{142,143}

Chiari Malformations

Chiari malformations are a group of defects affecting the cerebellum and brainstem. Three primary types have been described, types 1 through 3. Recently, clinicians have defined two more types of Chiari malformation: types 0 and 1.5. In type 0, there is little to no cerebellar herniation but an associated syringomyelia that regresses after posterior fossa decompression.^{144,145} Chiari type 1.5 describes a more severe form of Chiari type 1 in which descent of the medulla below the foramen magnum is seen in addition to a prominent cerebellar tonsillar herniation.¹⁴⁶ The controversial and rare Chiari type 4 (cerebellar hypoplasia) is often excluded but is associated with a small posterior fossa. It is important not to confuse secondary hindbrain herniation (hydrocephalus, tumors, lumbar cerebrospinal fluid diversion) with the primary types.

It remains unclear whether the three types have a common embryopathy. The common theme is an abnormally small posterior fossa. The degree of brainstem or cerebellar hernia may be due to physiologic factors; indeed, two theories have been proposed concerning Chiari type 2 malformations. The hydrocephalus hydrodynamic theory proposes that fetal hydrocephalus leads to an imbalance between supratentorial and infratentorial compartments, causing downward displacement of the hindbrain. The second theory, the traction model, proposes that the spinal cord is tethered, as in myelomeningocele, pulling the hindbrain caudally. Because the hindbrain hernia is reduced after fetal myelomeningocele repair, this theory has credence but does not explain other findings in Chiari malformations. Dysgenesis has been proposed to be the cause of the associated cortical findings in Chiari malformations and focal brainstem dysfunction. Furthermore, segmentation and segment identity genes have been implicated in the development of Chiari malformations because of the commonly associated skull base and upper cervical spine segmentation anomalies.¹⁴⁷

2.4 Editor's Comments

The authors describe our current understanding of the interactions of genes, proteins, and the resultant normal and abnormal neural development. They provide evidence that contradicts the classic teaching that the secondary neural tube develops from the transformation of caudal mesenchymal tissue to neural tissue and that lipomeningocele develops as a result of premature dysjunction. Despite burgeoning genetic knowledge, our understanding of most embryopathies remains “embryonic” but is maturing rapidly.

Pearls

- Maldevelopment of the CNS is typically coupled to malformations of another organ system.
- Induction plays an important role in neurodevelopment and occurs when a group of cells establishes, changes, or directs the development of an adjacent group of cells via direct contact or by secretion of diffusible molecules.
- Defects during gastrulation affect all three germ layers and include split-cord malformations; neurenteric, dermoid, and epidermoid cysts; spina bifida; intestinal malrotations, duplications, and fistulas; anterior meningoceles; other complex dysraphic malformations; and possibly congenital tumors such as teratomas.
- Primary neurulation is a complex process resulting in the development of the brain and spinal cord down to the S2 level, and can be divided into four events: neural plate formation and elongated by the process of convergent extension, neural plate midline bending, neural plate lateral wall bending, and neural fold fusion.
- Closure of the cranial neuropore with spinal canal occlusion isolates the ventricular system and increases the intraventricular pressure, which may drive brain enlargement.
- The closed anterior neuropore becomes the future site of the lamina terminalis.
- Nervous system segmentation in the antero-posterior axis is determined by the rostrocaudal gradients of homeotic genes such as gap genes, pair rule genes, and segment polarity genes.
- Open neural tube defects include anencephaly, craniorachischisis, myelomeningocele, and myeloschisis and reflect a variety of defects along the rostrocaudal axis during primary neurulation.
- Defects involving the dorsal ectoderm (dermal sinuses, dermoid and epidermoid cysts) likely results from incomplete dysjunction.
- Defects of secondary neurulation include abnormal filum terminale, terminal lipoma, and myelocystocele.
- Lipomyelomeningocele is believed to arise during primary neurulation, possibly by the process of premature dysjunction.
- The various types of Chiari malformations are likely embryologically different and require different clinical care.

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3 Neurologic Examination of the Newborn, Infant, and Child

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The ability to perform a thorough neurologic examination and to interpret the findings often obviates the need to perform imaging studies. Our purpose in this chapter is to facilitate understanding of the neurologic examination of children. For purposes of organization, the chapter is organized by age: examination of the newborn (0 to 4 weeks), the infant (1 to 24 months), and the older child (older than 2 years).

3.1 Components of the Neurologic Examination

3.1.1 Screening Methods

Interpretation of the neurologic examination findings depends on a thorough knowledge of normal childhood development. Examination of the term and preterm infant primarily reflects brainstem function and spinal cord reflexes, whereas examination of the older child approximates that of an adult. Maturation of the central nervous system (CNS) proceeds in a rostral to caudal fashion. For instance, head control develops first, with only a slight head lag on pull-to-sit at 4 months of age. The infant is able to sit supported at 6 months and then is able to pull to stand at 9 months. A video review of the neurodevelopmental milestones and the accompanying examination is available online at http://library.med.utah.edu/pedineurologicexam/html/home_exam.html.¹

Screening methods have been developed to assist the clinician in identifying those patients with developmental delays. The clinician has several screening tools at his or her disposal to screen for developmental delay. Each may identify different populations of children with developmental delay because each is characterized by different standardizations, comparison groups used for sensitivity and specificity, and population risk status.² For the purposes of a neurosurgical visit, broad general screening tools that address the main domains of fine and gross motor skills, language, adaptive behavior, and social skills are probably the best to use. There are two types of tools: directly administered scales, such as the Bayley Infant Neurodevelopmental Screen and the Denver-II (Glascoe), and questionnaires given to the family to complete, such as the Ages and Stages Questionnaires.³⁻⁵ The advantages of using these screening tests are that norms are stated explicitly and that normal development within each category is reassuring. However, as they reflect a snapshot in time of a child's development, they may not identify children with mild delays. Parent-based questionnaires may be better screens for mild developmental delay. Several studies have shown that parental reporting of current skills is predictive of developmental delay.⁴⁻⁶ The advantage of screens that rely on parental information is that they do not rely as heavily on the examination of a child who may be sick, afraid, drowsy, or noncompliant at the time of the visit.

In the school-age years, specific underlying abnormalities, such as learning disabilities, may become manifest as school

performance demands cognitive levels not assessed by screening tests. Cognitive development can be assessed, albeit imperfectly, by IQ testing, which can be a predictor of attention, social skills, maturational level, and intelligence. The Wechsler Intelligence Scale of Children-III, which tests verbal, performance, and full IQ, is the most commonly used measure of a child's intelligence. It is used for children ages 6 to 16 years, but some tasks may be difficult for children 6 to 7 years of age. Detailed neuropsychological testing may be necessary to evaluate cognitive function further.

Examiners should be cautioned, however, that a "normal screen" does not preclude subtle developmental abnormalities, as these screens focus narrowly on discrete milestones and do not assess fine detail within those parameters. In addition, a developmental screen assesses the patient's current developmental level and is not a predictor of future achievements or maximal potential. The real value of screening is to follow developmental milestones and to assess if a particular neurologic symptom is static or progressive over time.

3.1.2 History

In a neurologic examination, the examiner begins by taking the patient's history, which includes an outline of the evolution of the illness, its character, and the presence of similar illness in family members. The examiner attempts to establish neurologic disorders as progressive, intermittent, static, or saltatory. Static abnormalities noted in the first few months of life suggest congenital abnormalities or brain injuries sustained during the perinatal period. Progressive disorders suggest degenerative CNS disease, whereas abnormalities that are intermittent and alternate with return to normal neurologic function indicate paroxysmal disorders, primarily seizures. Saltatory disorders, characterized by exacerbation and partial recovery, are seen particularly with demyelinating and vascular diseases and with mitochondrial disorders.

Medical History

The medical history in the evaluation of children begins with the birth history. A complete pregnancy history is essential and should include the mother's age, number of pregnancies, number of deliveries, prenatal care, and number of induced and spontaneous abortions. The pregnancy history should be obtained with the intent of determining parameters that may present risks to the fetus, such as history of exposure to illness, maternal rash, maternal bleeding, maternal drug or alcohol use, and abnormal fetal growth. The history of labor and delivery is often a clue to the timing of a CNS injury. The examiner should note the type of anesthetic, if any, used for delivery of the child; duration of the rupture of membranes; whether or not there was meconium staining; fetal heart rate patterns if available; and finally, the child's Apgar scores. Gestational age should be noted, as this knowledge may impact interpretation of the newborn's neurologic examination.

Social History

The social history can provide clues to a neurologic diagnosis, such as exposures to toxins or medications. School reports may highlight specific cognitive difficulties that a child may have. The adverse effect of environmental risk factors, such as single parenthood, less than a high school education for one parent, limited parental contact, parental mental health concerns, and parental predilection for substance abuse, may be evident in the child's development.

Family History

Family history is important in many neurologic abnormalities. The presence of consanguinity, neurologic disorders, and systemic disease should be noted in family members. A family history of neonatal deaths is often a clue to metabolic disorders. A family history of seizures often points to the presence of one of the epilepsy syndromes. Neurocutaneous disorders are often inherited in an autosomal-dominant fashion, and family members should therefore be examined for neurocutaneous lesions, such as hypopigmentation and hyperpigmented macules, if a neurocutaneous disorder is suspected.

3.1.3 Physical Examination

CNS function depends upon normal function of all other body organs. Thus, abnormalities of other organ systems detected on examination are important. However, particular attention should be paid to abnormalities of hair, skin, teeth, and nails because they, like the brain, are of neuroectodermal origin and may reflect CNS lesions. For example, the pattern of hair growth reflects underlying brain development, so that the absence of a posterior hair whorl or the presence of multiple hair whorls suggests an abnormality in prenatal brain growth. Neurocutaneous abnormalities, such as café au lait spots, neurofibromas, and port wine stains, occur in several CNS disorders, such as tuberous sclerosis, neurofibromatosis, and Sturge-Weber syndrome, respectively. Therefore, the child's entire skin surface should be examined during the physical examination. Weight, height, and head circumference should routinely be measured. At birth, head circumference is approximately 35 cm, with growth at a rate of 2 cm per month from 0 to 3 months and 1 cm per month from 3 to 6 months of age. Intrauterine insults and many genetic syndromes associated with below- or above-average size have been linked with developmental delay. Microcephaly and macrocephaly are red flags for developmental problems with underlying structural CNS pathology, especially in the context of genetic or acquired disorders. As long as the head circumference is within normal limits, the size of the anterior fontanel is of little concern. Conditions that may lead to a large anterior fontanel include hypothyroidism, trisomy syndromes, in utero malnutrition, hypophosphatemia, rickets, osteogenesis imperfecta, and hydrocephalus.

3.2 Neurologic Examination of the Neonate

The formal neurologic evaluation includes an assessment of mental status, cranial nerves, motor system, sensory system, cerebellar function, and reflexes.

3.2.1 Mental Status Evaluation

The mental status examination of the neonate is made by the observation of spontaneous eye opening; movements of the eyes, face and extremities; and response to stimulation. Although both normal-term and preterm infants spend a large proportion of time in sleep, activity during wakefulness and duration of sleep vary with age. For instance, awake and sleep states are difficult to distinguish in a preterm infant born before 28 weeks of gestation. After 32 weeks of gestation, there is an increase in the frequency and duration of alertness. The normal-term newborn is easily aroused to a state in which the eyes are open and blink at a strong light stimulus. The ability to visually fix and follow at or after 34 weeks is a reassuring finding. To assess if a baby is visually fixing, the examiner should look for arrest of other activity, such as sucking. An astute examiner can observe subtle changes in mental status; an irritable infant will appear agitated, spontaneously cry, or cry to minimal stimulation and will not be easily soothed. The lethargic infant will have delayed or poorly maintained responses to stimulation.

3.2.2 Cranial Nerve Examination

Cranial Nerve I

Olfaction cannot be reliably assessed at bedside in the neonate.

Cranial Nerve II

Vision may be tested with the infant's blink response to a strong light stimulus. The blink response can be predictably elicited beyond 30 weeks of gestation. The ability of the infant to fix visually on a face and follow it is reassuring for the assessment of normal visual acuity. Visual fields are not reliably assessed in neonates. The pupillary response to light is predictably present beyond 29 weeks of gestation. Funduscopic examination may demonstrate the presence of congenital malformations involving the eye or retina. Placing a pacifier in the child's mouth may aid in keeping the eyes open during the examination. A direct and consensual pupillary response should be present. An afferent pupillary defect can be detected even at this young age by swinging the light from eye to eye and noting pupillary dilation when the light is brought to bear on the involved optic nerve.

Cranial Nerves III, IV, and VI

By 34 weeks of gestation, an infant will be able to fix and follow an object with his or her eyes, particularly the mother's face. Another maneuver to test extraocular movements is to stimulate the vestibulo-ocular reflexes by gently spinning the infant. The baby is held in front of and slightly above the examiner and spun to the right or left. There should be conjugate eye deviation in the direction in which the examiner spins the child. After cessation of spinning, post-rotational nystagmus in the opposite direction is noted for a brief period, after which the vestibular response is ablated by visual fixation. This technique allows the examiner to assess vestibular function, the presence of intact extraocular muscle function, and visual acuity with a single procedure. Of note, disconjugate gaze is common in normal newborn infants when they are not fixing on objects.



Fig. 3.1 (a) Congenital absence of the depressor anguli oris seen during smiling in early infancy. (b) Same patient as a toddler.

Cranial Nerve V

In neonates, the muscles of mastication can be assessed by watching the infant suck and swallow. The corneal reflex may be assessed at the end of the evaluation.

Cranial Nerve VII

Facial symmetry at rest and during sucking activity is used to assess facial nerve function. One should also note facial symmetry during crying. Congenital absence of the depressor anguli oris, a disorder that mimics facial nerve lesions, is noted only during smiling or crying (► Fig. 3.1a,b and ► Fig. 3.2).

Cranial Nerve VIII

The vestibular portion of cranial nerve VIII can be assessed by spinning the infant as described in the examination of cranial nerves III, IV, and VI. Hearing can be grossly evaluated by the presence of a blink elicited by a sharp sound, such as a bell directed at either ear. Vestibular function mediated by the vestibulocochlear nerves is tested by caloric stimulation. The head is angled at 30 degrees, orienting the horizontal semicircular canals vertically, and the external canal is inspected for cerumen or defects of the tympanic membrane. Ten milliliters of ice water is then instilled into the ear, and the resulting eye movements are observed. In the conscious patient, coarse nystagmus develops toward the ipsilateral ear



Fig. 3.2 Neonatal right peripheral facial palsy.

without eye deviation. In the comatose patient, the fast component is depressed, and the eye becomes tonically deviated ipsilaterally.

Cranial Nerves IX and X

The gag reflex can be reliably elicited beyond 30 weeks of gestation. The quality of the infant's cry may be abnormal in many neurologic as well as genetic disorders.

Cranial Nerve XI

Sternocleidomastoid function and trapezius function are best assessed in the neonate by detecting shoulder droop, by noting a preferential position of the infant’s head and decreased spontaneous activity of the shoulders, or both.

Cranial Nerve XII

Tongue movements of the normal newborn are such that fasciculations are difficult to recognize, but atrophy, tongue deviation, or both, can be appreciated.

3.2.3 Motor Examination

Normal newborn motor function varies with gestational age (► Table 3.1). From 28 to 40 weeks, with myelination of subcortical motor pathways from the brainstem, the infant develops increasing flexor tone in the legs, with increasing flexor tone spreading rostrally. After 40 weeks, with progressive myelination of the corticospinal tracts, there is a progressive “unfolding” from the flexor tone of the neonate to balanced flexor–extensor tone, increasing voluntary control of axial and extremity muscles, and refinement of movements in a rostral to caudal, proximal to distal fashion. The newborn motor examination is best achieved through the

observation of spontaneous motor activity, tone, and posture. Overall, the term infant’s movements are of small amplitude and rapid frequency, whereas those of a preterm infant are slow and athetoid in quality.

At 28 weeks of gestation, the normal posture of the preterm infant is flexion of the lower extremities with partial abduction at the hip and extension of the upper extremities. Abnormal postures, such as extension of the lower extremities in the term infant or flexion of the upper extremities in the premature infant, indicate hypertonia. Grasping the infant’s arms and pulling the infant to a sitting position allows examination of cervical tone. The normal preterm infant has profound head lag with little to no neck flexion. In contrast, the term infant has both extension and flexion of the neck if normal strength is present. Tone can also be assessed through the vertical and horizontal suspension maneuvers. In the vertical suspension maneuver, the infant is held under the axilla. The hypotonic infant will slip through the examiner’s hands. In the horizontal suspension maneuver, support is held under the trunk with the infant in the prone position. The normal infant can hold the head up and flex the limbs against gravity with the back held relatively straight. The hypotonic infant, when held in this position, will form a u-shape characteristic of hypotonia. Of note, because infants function primarily at the level of the rubrospinal, vestibulospinal, and reticulospinal pathways, they can have significant hemispheric dysfunction with relatively few deficits on the neurologic examination.

Table 3.1 Summary of the neurologic examination with respect to gestational age

	28 weeks	32 weeks	34 weeks	40 weeks	Red flags
Mental status	Needs gentle rousing to awaken	Opens eyes spontaneously; sleep–wake cycles apparent		At 36 weeks ↑ alertness, cries when awake	-Irritable or lethargic infant
Cranial nerves					
Pupils	Blinks to light	Consistent pupillary reflex	Fix and follow		-No response to auditory stimulus -“Chomp suck”: clamps down on pacifier but no suck (bulbar dysfunction)
Hearing	Pauses, no orientation to sound			Head + eyes turn to sound	
Suck + swallow	Weak suck, no synchrony with swallow	Stronger suck, better synchrony with swallow		Coordinated suck + swallow at 37 weeks	
Motor					
Posture	Minimally flexed	Flexed hips and knees	↑ Flexion at hips and knees	Flexed in all extremities	-Hypotonia -Hypertonia
Neck flexion	0	0	0	Fair	-28-Week infant with jerky movements -Full-term infant with writhing movements
Reflexes					
Moro reflex	Weak, incomplete hand opening	Complete extension + abduction		Full Moro reflex (with anterior flexion)	-Asymmetry -If obligatory or sustained, suggests pyramidal or extrapyramidal motor abnormality
ATNR	Present but weak	Present, involves arm		ATNR appears at 35 weeks	-Fixed obligate grasp (suggests bilateral hemispheric dysfunction.)
Palmar grasp	Present with reinforcement	Present without reinforcement	Grasp stronger	Strong grasp, able to be lifted out of bed	
Rooting			Present	Present	

Abbreviation: ATNR, asymmetric tonic neck reflex.

Source: Adapted from Koenigsberger MR. Judgment of fetal age. *Pediatr Clin North Am* 1966;13:823–833.⁷

3.2.4 Sensory Examination

The full sensory examination assesses sensation to light touch, pinprick, temperature, vibration, and proprioception but is difficult to perform completely in neonates. Sensation can be grossly tested with pinprick and by observation of the neonate's response, either facial grimace or withdrawal of an extremity, to the stimulus beginning at 28 weeks of gestation. In an infant who is feeding, interruption of the sucking rhythm indicates perception of the sharp stimulus.

3.2.5 Reflexes

Beginning at 33 weeks of gestation, the Achilles, patellar, biceps, brachioradialis, and pectoral reflexes can be elicited. Myotactic reflexes are elicited with sudden tendon stretch by percussion over the tendon. The muscle itself should not be percussed, because muscle contraction occurs even in the presence of lower motor neuron lesions. The plantar response is a nociceptive reflex elicited by noxious stroking of the lateral aspect of the plantar surface from the heel toward the toes. This is not a helpful response to elicit in newborns as the response can be flexor or extensor, depending on the technique used to elicit the response. Unsustained clonus at the ankle (<8 beats) is normal if symmetrical, but sustained clonus is suspect at any age.

Primitive Reflexes

Several primitive reflexes evolve with maturation of the CNS and reflect the functional integrity of the brainstem. As a group, they tend to be symmetric, and they are modified with age, reflecting the normal maturation of descending inhibitory cerebral influences. Persistence of these reflexes indicates improper maturation of brain structures or injury (see ► Table 3.1).

The full Moro reflex consists of bilateral hand opening with upper extremity extension and abduction, followed by anterior flexion of the upper extremities, then an audible cry. This is best elicited by dropping the infant's head in relation to the body into the examiner's hands, but any sudden change in position will elicit this reflex. The Moro reflex, which is mediated by the vestibulospinal pathway, is fully elicited at 28 weeks of gestation and disappears at 4 to 6 months of age.

The asymmetric tonic neck reflex (ATNR) is elicited by rotating the head to one side, with subsequent elbow extension to the side toward which the head is turned and elbow flexion on the side of the occiput (► Fig. 3.3). This reflex also disappears at 4 to 6 months of age. An obligate ATNR is always abnormal and indicates bilateral hemispheric dysfunction with lack of brainstem inhibition of this reflex.

The palmar grasp, mediated by brainstem vestibular nuclei, is elicited by placing a finger in the palm. This results in flexion of the infant's hand, with flexion of the elbow and shoulders. Persistence of this response beyond 4 to 6 months is abnormal (see ► Table 3.1).

3.3 Neurologic Examination of the Infant

The neurologic examination of the child beyond the newborn period can be challenging, especially as stranger anxiety peaks



Fig. 3.3 Asymmetric tonic neck reflex.

between 18 and 24 months of age. However, stranger anxiety is a normal phenomenon, and its presence signals cognitive development. There are various approaches to examining children in this age range. As a rule, the direct approach of examining a child starting with the head and finishing with the feet is doomed to failure. On the other hand, observation of the child interacting with toys or family members allows the examiner to glean much of the information needed about the child's neurologic status. Invasive aspects of the examination, such as the fundoscopic examination, are performed last. In our experience, more information is obtained from observation of a child than from auscultation, palpation, percussion, testing of reflexes, sensory testing, and ophthalmologic examination.

3.3.1 Mental Status Evaluation

The evaluation of mental status in the infant is, as in the neonate, performed by observation of spontaneous activities, feeding behavior, and interaction with the environment. Language can be assessed as well by noting the use of gestures, such as pointing or shaking the head to indicate wants.

3.3.2 Cranial Nerve Examination Cranial Nerve I

Once the child has developed speech, olfactory function can be tested. Oils such as clove and peppermint can be used to assess

perception of smell. Highly volatile substances, such as ammonia, should not be used because they are irritating and test cranial nerve V function at the level of the nasal mucosa rather than olfaction.

Cranial Nerve II

By 6 months of age, visual acuity has been found to be 20/20 by visual evoked potentials. During the examination, visual acuity can be estimated to be grossly normal if the infant can visually locate and track a small object. Peripheral vision can be tested by bringing an object into the visual field from behind the child.

Cranial Nerves III, IV, and VI

In the older infant and child, extraocular movements can be easily assessed by having the infant visually follow an object of interest. The third nerve innervates the medial rectus, superior and inferior rectus, inferior oblique, and levator muscles of the upper eyelid and supplies the parasympathetic constrictor fibers to the pupil. A parasympathetic lesion results in pupillary dilatation, whereas a sympathetic lesion results in a small, myotic pupil. The fourth cranial (trochlear) nerve innervates the superior oblique muscle, which depresses and intorts the eye. Weakness of this muscle results in head tilt to the opposite shoulder as compensation for the lack of intorsion. The sixth cranial nerve innervates the lateral rectus muscle, which abducts the eye. Abnormalities of cranial nerves III, IV, or VI may cause diplopia. In the infant, this may cause such subtle signs as irritability or may be overtly manifest in the child who covers an eye to view objects.

Supranuclear lesions involving the corticobulbar pathways that innervate the third, fourth, and sixth nerve nuclei result in abnormalities of volitional gaze. Pursuit movements are intact, but saccadic movements are severely impaired. The patient cannot volitionally change eye direction and must use vestibulo-ocular reflexes to move the eyes. Children with these abnormalities close their eyes to break fixation and turn the head in the direction opposite that toward which eye movement is desired. Once the object of interest enters the visual field, the child opens the eyes, fixes on the object, and then uses pursuit movements to bring the object into binocular fixation. The disorder is known as oculomotor apraxia. Intranuclear ophthalmoplegia, in which there is paresis of the adducting eye and nystagmus of the abducting eye, is due to lesions of the medial longitudinal fasciculus. Paralysis of upward gaze is seen in lesions of the periaqueductal gray matter.

In the infant, deviation of the eye may be observed. Misalignment of the visual axes is referred to as strabismus and may be secondary to phoria or a tropia. Phorias are held latent by sensory fusion but can be elicited with the cover-uncover test. When an infant uses binocular vision to fix on an object, the phoria disappears. When one eye is covered, however, the eye seeks a position at rest and deviates from the axis of the other eye. When the eye is uncovered and binocular vision is reestablished, the eyes realign. The slight movement of the eye indicates that a phoria is present. Tropias are deviations of the eye noted at rest that cannot be overcome by fusion. Both phorias and tropias are further defined according to the direction of deviation with the prefix *eso-* (if the eye turns inward) or *exo-*

(if the eye turns outward). If the eye movements are full and conjugate, the strabismus is nonparalytic and indicates that a supranuclear gaze abnormality is present. On the other hand, if there is limitation of eye movement, the strabismus is paralytic and indicates a nuclear or infranuclear lesion.

Cranial Nerve V

The masseter muscles can be palpated, and jaw deviation can be assessed by simple observation. The trigeminal nerve additionally can be assessed by testing sensation with a cotton wisp over the face in the distribution of the V₁, V₂, and V₃ branches of the trigeminal nerve.

Cranial Nerve VII

Symmetry of facial movement in the examination of infants of this age can be assessed both at rest and during smiling, crying, or grimacing. Taste testing is reliable.

Cranial Nerve VIII

The infant begins to localize sound at 4 months.

Cranial Nerves IX and X

The gag reflex is easily assessed at the end of the examination.

Cranial Nerve XI

As in the newborn, shoulder droop or head tilt is indicative of dysfunction of the sternocleidomastoid and trapezius muscles.

Cranial Nerve XII

In the infant, fasciculations, tongue atrophy, and tongue deviation can be assessed. Specific tongue movements can be assessed at 1 year of age by having the child follow a tongue depressor with the tongue.

3.3.3 Motor Examination

Tone and Posture

The best way to examine the infant is by observation of the infant lying quietly on the examination table. The presence of unusual posturing of the limbs may indicate basal ganglia lesions. Tone and passive range of motion of the extremities will provide information regarding spasticity and rigidity. Spasticity is characterized by a “clasp knife” response, with resistance to passive stretch and sudden release at a critical point. Resistance to passive stretch is encountered through the entire arc in rigidity. Assessment of the infant’s posture is very age-dependent. The child is able to lift the head off the examination table at 2 months of age and lift both head and chest off the table at 3 months of age. Crawling is seen at 9 to 12 months of age. The child can reach at 4 to 5 months of age, and most infants can sit unsupported at 7 months. At 12 to 15 months of age, the child can walk independently, but the gait is broad-based and unsteady. The base narrows to a few inches at 6 years.

Assessment of Muscle Bulk

Bulk is assessed by palpation, observation, and comparison with the contralateral limb. Atrophy can eventually occur with extrapyramidal and pyramidal lesions but is most pronounced with lower motor neuron lesions.

Assessment of Muscle Strength

Quantitative assessment of muscle strength is difficult in this age group. A few maneuvers in the examination can help the examiner assess the infant's strength. By holding the infant in the axilla and noting the resistance in the trunk when lifting the child, the examiner can assess upper extremity strength. To test lower extremity strength, the examiner can note whether the infant can bear weight on the legs if supported. However, strength is best evaluated by observation of the child's functional activity. For example, arm and shoulder strength can be assessed by observing the infant in the prone position and the ability to raise the head off the examination table by pushing with the arms. Muscle weakness of pyramidal origin is spastic, whereas extrapyramidal weakness is rigid. Flaccidity is seen with lower motor neuron disease. The development of a definite hand preference before 24 months of age suggests that a lesion is present in the CNS or the peripheral nerves of the opposite limb. Fine motor development is indicated by the appearance of a pincer grasp at the age of 9 months (► Fig. 3.4).

3.3.4 Cerebellar Examination

Gait should also be tested in those children who are ambulatory, but the examiner should remember that gait varies with the child's age. Gait progressively narrows during early childhood. Formal cerebellar testing is difficult in the infant, as it requires some playful interaction between the examiner and the infant. Observation of the infant sitting alone may be helpful, as truncal sway may indicate cerebellar dysfunction. Titubation of the head may also be present. Fine motor coordination can be tested by having the child reach for objects and noting signs of tremor or dysmetria.



Fig. 3.4 A pincer grasp in a normal 9-month-old infant.

3.3.5 Sensory Examination

Sensory testing in this age group must be performed with care. The infant usually responds to light touch by looking at the stimulus source and withdrawing the extremity. A vibratory stimulus is perceived by most infants as a startle and is quite different from touch. Proprioception cannot be directly evaluated, but posture and gait are often clues to abnormalities of proprioception. Pain sensation can be assessed by using a pin, but this should be performed late in the examination, and the pin should be hidden from the child. If the child sees the pin early in the process, any productive interaction between examiner and patient will be lost.

3.3.6 Primitive Reflexes

The primitive reflexes were described in the discussion of the neonate. As previously noted, of particular importance in this age group is documentation of the appearance and disappearance of these primitive reflexes, as they reflect the maturation of the CNS (see ► Table 3.1). For instance, the plantar grasp, which appears at birth, usually disappears by age 9 to 10 months. The continued presence of this response interferes with the progression to weight bearing on the legs and ultimately walking. The ATNR should not persist beyond 6 months of age. Persistence of this response interferes with sitting or standing.

Failure to develop certain responses also indicates that abnormalities are present. The parachute response appears after 6 to 8 months of age and is mediated by the brainstem vestibular nuclei. This response persists throughout life in modified forms. It can be tested by tilting a sitting infant to either side, which results in extension of the ipsilateral arm in a protective fashion (► Fig. 3.5). The response can also be elicited by picking up the infant and thrusting the infant's head toward the examining surface, with resultant bilateral extension of both upper extremities. A child who does not exhibit a parachute response is unlikely to walk in the near future, and failure to develop a parachute response can be a predictor of whether a child will develop the ability to walk.

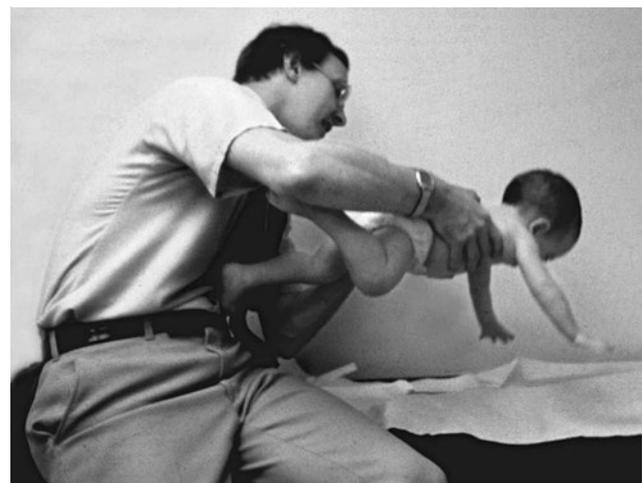


Fig. 3.5 The parachute response in a normal 9-month-old infant.

3.4 Examination of the Older Child

3.4.1 Mental Status Evaluation

In the older child, language can be specifically tested, including speech, reading, and writing. Dysarthria refers to abnormalities of the speech mechanism, which is mediated by the hypoglossal, vagus, facial, and trigeminal nerves. Receptive aphasia refers to impairment of language comprehension and reception, occurring with lesions in the posterior superior temporal lobe gyrus in the Wernicke area. Impairment of speech production and fluency results in expressive aphasia, which occurs with lesions of the posterior inferior frontal lobe gyrus, or Broca area. Conduction aphasia results in the ability to repeat but not to name objects. This occurs with lesions of the arcuate fasciculus, which connects the Broca and Wernicke areas. Calculation is a dominant-hemisphere function residing in the angular gyrus. In a child about the age of 7 years, calculations can be assessed by asking the child to subtract numbers. The nondominant hemisphere can be tested by using picture drawings to assess visual spatial function. Memory can be tested beginning at 4 to 5 years of age, when a child is able to remember four digits. The normal adult can remember seven or eight digits.

3.4.2 Cranial Nerve Examination

Cranial Nerve I

Each nostril is tested individually with occlusion of the contralateral nostril. The child is asked to name the perceived smell. This test is best performed at the age of 6 years, as the child is sufficiently verbal then to comply with the examination.

Cranial Nerve II

Examination of the optic nerve can be divided into visual acuity, funduscopic examination, and visual fields. By the age of 4 years, a child can cooperate well enough to use a visual acuity chart. Visual fields can be evaluated with a white or red test object or with double simultaneous stimulation in both visual fields.

Cranial Nerves III, IV, and VI

The oculomotor, trochlear, and abducens nerves are examined in much the same way as they are in infants and neonates.

Cranial Nerve V

In the older child, the sensory distributions of V_1 , V_2 , and V_3 can be accurately delineated. The trigeminal nerve is tested by noting jaw deviation and palpating the masseter muscles.

Cranial Nerve VII

The motor function of the facial nerve is assessed as described above. In addition, taste sensation over the anterior two-thirds of the tongue can be tested after the age of 6 years with salt and sugar sensations. However, it is important to be certain that the

patient is able to identify whether or not the test solution is salt or sugar. Once the tongue is back in the mouth, the solution is spread to the distribution of the contralateral seventh nerve, as well as of the ninth and tenth cranial nerves posteriorly.

Cranial Nerve VIII

The auditory component of the vestibulocochlear nerve, hearing, can be tested in the older child with a whisper. The best technique is to use spondee words—that is, words with equally accented syllables or one syllable, such as “cowboy” and “night-light.” These words are whispered at a distance of 2 feet while the opposite ear is masked. Vestibular function mediated by the vestibulocochlear nerve is tested by caloric stimulation as previously described

Cranial Nerves IX and X

The gag reflex is tested as described in the infant.

Cranial Nerve XI

In the older child, a shoulder droop or a head turning may be detected with lesions of cranial nerve XI. The upper fibers of the trapezius can be palpated as the child attempts to elevate the outstretched arms against resistance. The sternocleidomastoid muscle is palpated as the child attempts to turn the neck against resistance.

Cranial Nerve XII

In the older and cooperative child, fasciculations and atrophy are more easily appreciated. In children with a lower motor neuron lesion of the hypoglossal nerve, the tongue deviates in the direction of involvement of the hypoglossal nerve or nucleus, and in an upper motor neuron lesion, it deviates in the direction opposite that of cerebral hemispheric involvement.

3.4.3 Motor Examination

Assessment of mass, strength, and tone comprises the motor evaluation of the older child. Strength is tested as resistance against passive movement by the examiner and, in the older child, can be assessed quantitatively. It is traditionally graded from 0 to 5. A grade of 0 indicates no movement, 1 indicates a flicker of movement, 2 indicates movement with gravity eliminated, 3 indicates the ability to move against gravity but minimal resistance, 4 indicates the ability to move against some resistance, and 5 indicates normal power. Innervation of specific muscles is listed in ► Table 3.2 and ► Table 3.3.

3.4.4 Cerebellar Examination

The child should be observed standing, starting to walk, stopping, and turning, along with the associated limb movements. These movements require the coordination of sensory, motor, cerebellar, visual, and vestibular functions. For example, a wide-based gait may be seen with disorders of the neuromuscular junctions, peripheral nerves, and muscles because of weakness. Therefore, observation of a wide-based gait should

Table 3.2 Root innervation of major upper extremity muscles

Root	Muscle	Nerve
C3 C4	Trapezius	Spinal accessory
C4 C5	Rhomboids	Brachial plexus
C5 C6	Supraspinatus	Dorsal scapular
C5 C6	Infraspinatus	Suprascapular
C5 C6	Brachioradialis	Suprascapular
C5 C6 C7	Serratus anterior	Radial
C5 C6 C7	Pectoralis major (clavicular)	Long thoracic
C6 C7 C8 T1	Pectoralis major (sternal)	Lateral pectoral Medial pectoral
C5 C6	Deltoid	Axillary
C5 C6	Biceps brachii	Musculocutaneous
C6 C7 C8	Triceps	Radial
C5 C6	Brachioradialis	Radial
C6 C7	Extensor carpi radialis longus	Radial
C7 C8	Supinator	Posterior interosseous
C7 C8	Extensor digitorum communis	Posterior interosseous
C7 C8	Extensor indicis proprius	Posterior interosseous
C6 C7	Flexor carpi radialis	Median
C6 C7	Pronator teres	Median
C8 T1	Abductor pollicis brevis	Median
C8 T1	Opponens pollicis	Median
C8 T1	Lumbricals I & II	Median
C7 C8	Pronator quadratus	Anterior interosseous
C7 C8	Flexor digitorum profundus I & II	Anterior interosseous
C7 C8	Flexor pollicis longus	Anterior interosseous
C7 C8 T1	Flexor carpi ulnaris	Ulnar
C7 C8	Flexor digitorum profundus III & IV	Ulnar
C8 T1	Abductor digiti minimi	Ulnar
C8 T1	Palmar interossei	Ulnar
C8 T1	Dorsal interossei	Ulnar

Note: Bold type indicates predominant root innervation.

prompt a work-up, not only for cerebellar disease but also for other lesions that may affect the gait. Rapid alternating movements should also be tested as a part of the cerebellar examination. In cerebellar disease, the rate, amplitude, direction, and strength will be diminished. Abnormalities in performing rapid alternating movements may also be seen in extrapyramidal disease, with diminished rate and amplitude, and in corticospinal disease, with diminishing amplitude of successive movements. Dysmetria, an error in measuring distances, may be noted, as well as intention tremor during finger-to-nose or heel-to-knee-to-shin movements.

3.4.5 Sensory Examination

The full sensory examination assesses sensation to light touch, pinprick, temperature, vibration, and proprioception. Cooperation is essential in assessing sensory function in children. The examination should not be relied upon if there is any doubt as to the child's cooperation. In most children beyond the age of 6 years, a useful screening sensory examination of the hands can be performed by asking the child to distinguish between coins, particularly a penny and a dime. If these functions are intact, it

Table 3.3 Root innervation of major lower extremity muscles

Root	Muscle	Nerve
L2 L3 L4	Iliopsoas	Femoral
L2 L3 L4	Rectus femoris	Femoral
L2 L3 L4	Vastus lateralis	Femoral
L2 L3 L4	Vastus intermedius	Femoral
L2 L3 L4	Vastus medialis	Femoral
L2 L3 L4	Adductor longus	Obturator
L2 L3 L4	Adductor magnus	Obturator
L4 L5 S1	Gluteus medius & gluteus minimus	Superior gluteal
L4 L5 S1	Tensor fasciae latae	Superior gluteal
L5 S1 S2	Gluteus maximus	Inferior gluteal
L5 S1	Biceps femoris	Sciatic
L4 L5 S1	Medial hamstrings	Sciatic
L5 S1 S2	Lateral gastrocnemius	Tibial
S1 S2	Medial gastrocnemius	Tibial
S1 S2	Soleus	Tibial
L5 S1	Tibialis posterior	Tibial
L5 S1 S2	Flexor digitorum longus	Tibial
L5 S1 S2	Abductor hallucis brevis	Tibial
S1 S2	Abductor digiti minimi quinti	Tibial
L4 L5	Tibialis anterior	Deep peroneal
L4 L5	Extensor digitorum longus	Deep peroneal
L4 L5 S1	Extensor hallucis longus	Deep peroneal
L4 L5 S1	Extensor digitorum brevis	Deep peroneal
L5 S1	Peronei	Superficial peroneal

Note: Bold type indicates predominant root innervation.

Source: Adapted from O'Brien M. Aids to the Examination of the Peripheral Nervous System. New York, NY: W. B. Saunders; 2010:62–66.⁸

assures the examiner that the peripheral receptors, peripheral nerves, dorsal root ganglia, spinal cord pathways, and thalamic and parietal cortical sensory systems are intact. If abnormalities are suggested in this task, then the examiner must perform detailed testing of individual sensory modalities. Segmental sensory innervations are mapped according to a dermatomal chart (► Fig. 3.6, ► Fig. 3.7, ► Fig. 3.8, ► Fig. 3.9). If all sensory pathways are intact but the patient is unable to identify objects presented, astereognosis is present, indicating a lesion of the parietal lobe.

3.4.6 Reflexes

Reflexes are graded from 0 to 4+, with absence of a reflex recorded as 0 and normal reflexes as 2+. If clonus is elicited, reflexes should be graded as 4+. Reflexes may be involuntarily diminished by muscle contraction, so distraction techniques should be used when this is suspected. After the age of 2 years, the plantar response is consistently flexor. The extensor, or Babinski, response is characterized by extension of the great toe and fanning of the other four plantar digits and is a sign of corticospinal tract lesions.

3.5 Editor's Comments

This chapter is one of the most important in the entire book. It is incumbent on pediatric neurosurgeons to distinguish normal

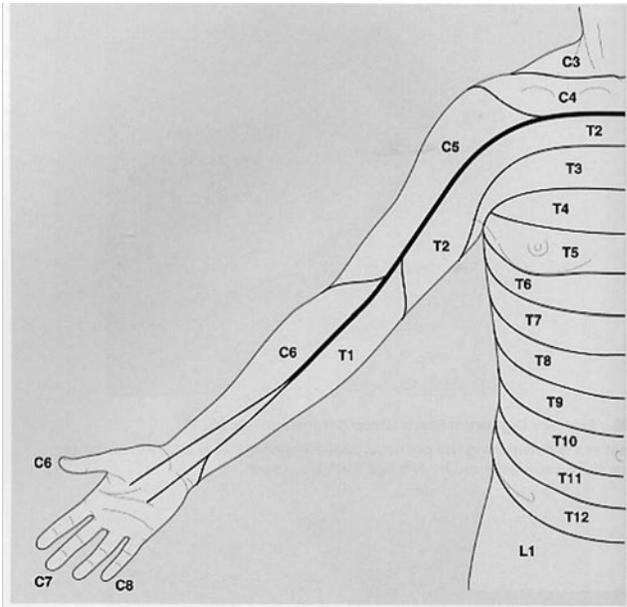


Fig. 3.6 Approximate distribution of dermatomes on the anterior aspect of the upper limb. (Reprinted with permission of the publisher from Brain. Aids to the Examination of the Peripheral Nervous System. Amsterdam, the Netherlands: Elsevier; 2000:56–57. © 2000.)

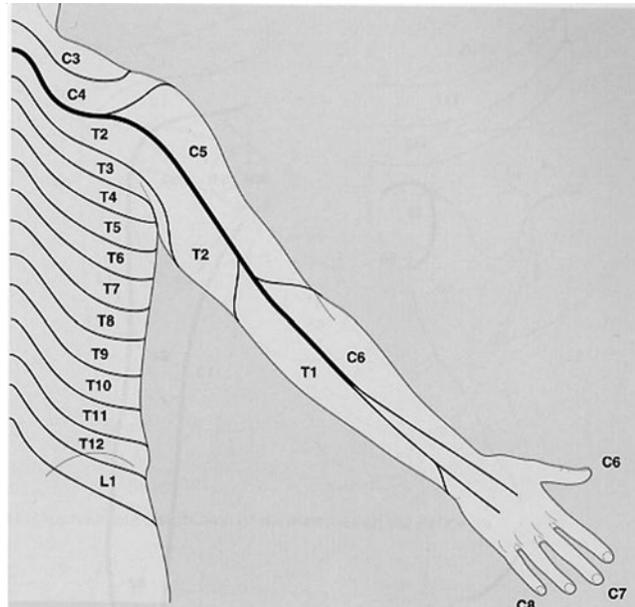


Fig. 3.7 Approximate distribution of dermatomes on the posterior aspect of the upper limb.⁸ (Reprinted with permission of the publisher from Brain. Aids to the Examination of the Peripheral Nervous System. Amsterdam, the Netherlands: Elsevier; 2000:56–57. © 2000.)

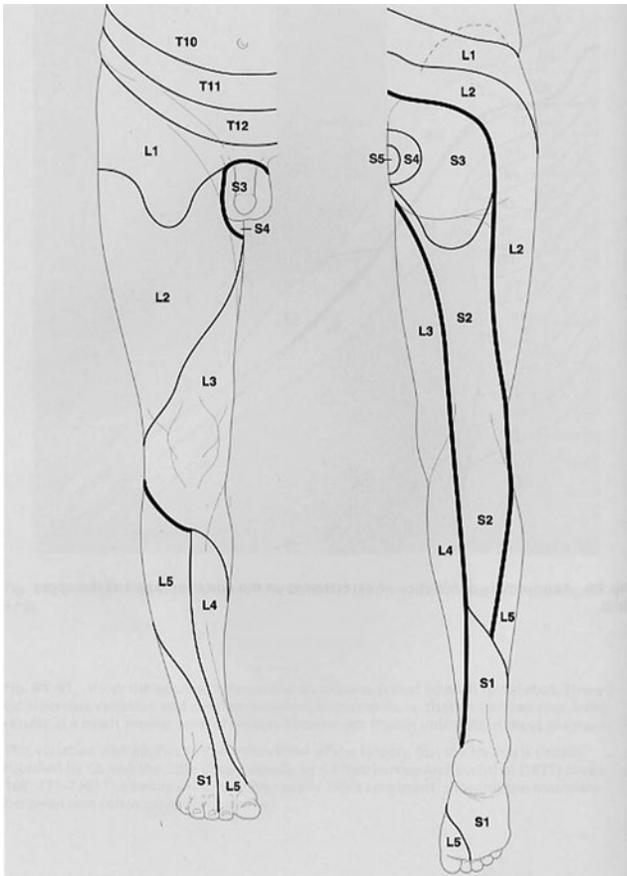


Fig. 3.8 Approximate distribution of dermatomes on the lower limb. (Reprinted with permission of the publisher from Brain. Aids to the Examination of the Peripheral Nervous System. Amsterdam, the Netherlands: Elsevier; 2000:58–59. © 2000.)

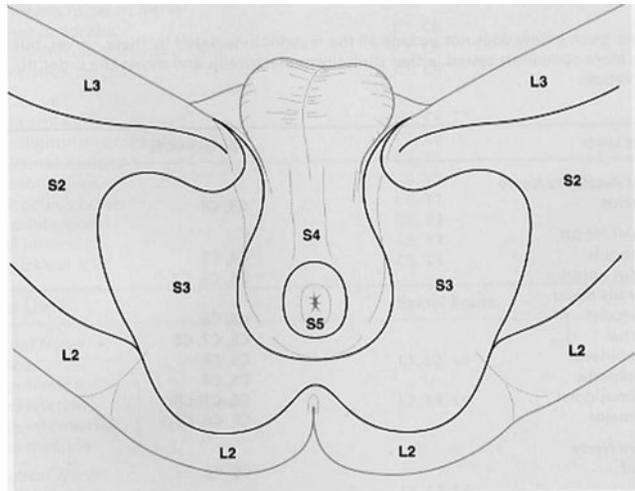


Fig. 3.9 Approximate distribution of dermatomes on the perineum.⁸ (Reprinted with permission of the publisher from Brain. Aids to the Examination of the Peripheral Nervous System. Amsterdam, the Netherlands: Elsevier; 2000:58–59. © 2000.)

from abnormal development, to know that several beats of ankle clonus in a newborn are normal but that the development of handedness in a 2-year-old is abnormal. The authors note that a careful neurologic examination of an infant or child may avoid unnecessary tests; that is true, but more importantly, it gives information about the function of a child's immature nervous system, information that aids the interpretation of neuroimaging.

Pearls

- More information is obtained from observation of a child than from auscultation, palpation, percussion, testing of reflexes, sensory testing, and ophthalmologic examination.
- Stranger anxiety in the toddler makes for a difficult examination but is an indicator of cognitive development.
- Knowledge of normal developmental milestones is essential to interpretation of the neurologic examination.
- Hand preference before the age of 2 years is abnormal.
- A child who does not exhibit a parachute response is unlikely to walk in the near future.

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4 Caring for the Pediatric Neurosurgical Patient

Stephanie Greene

The care of pediatric neurosurgical patients is a broad and challenging topic. This chapter deals principally with general guidelines for the management of these children, from measures to reduce infection to pain control regimens to efforts to limit postoperative complications. Specific topics are addressed in considerably more detail in individual chapters.

4.1 Preoperative and Perioperative Management

4.1.1 Patient Preparation for Surgery

Patients at Children's Hospital of Pittsburgh are requested to use a chlorhexidine gluconate shampoo and body wash (4% w/v chlorhexidine gluconate; Hibiclens) for five consecutive nights leading up to the surgical date for all elective procedures. Although the Cochrane Database guidelines do not recommend preoperative body washing to reduce surgical site infections (SSIs; commonly used abbreviations are listed in ► Table 4.1), those guidelines are based on data from 20 to 30 years ago.¹ Multiple studies with sample sizes too small to achieve statistical significance have found lower numbers of colony-forming units (CFUs) on the incisions, on the intraoperative cultures, and on the skin of patients who showered preoperatively with chlorhexidine gluconate.²⁻⁵ Multiple days of showering have been recommended, with the most important day being the day before surgery.^{6,7} The preoperative skin preparation should be the same preparation used in the operating room (OR) immediately before surgery, as the effect of exposure to a skin preparatory product is cumulative.⁸

Hair clipping should be minimal and should be performed just before skin preparation in the OR. Clipping hair in the days before surgery may lead to an increased incidence of infection, although data have not been statistically significant.^{9,10} Shaving should not be performed, as infection rates are clearly higher.^{9,11,12} The avoidance of hair clipping is associated with a slightly lower rate of postoperative infection, and some have suggested that no hair removal be performed.¹³⁻¹⁵

Skin preparation before incision is not performed in a uniform fashion around the country. Chlorhexidine gluconate (2% chlorhexidine gluconate, 70% isopropyl alcohol) achieves greater reduction of skin microflora than does povidone-iodine and has greater residual activity after a single application.^{2,16,17} Ethanol produces faster bactericidal activity, and at high concentrations it is the most effective product against viruses. However, its flammability makes it a less desirable option in the OR.¹⁸ Preoperative skin antisepsis with chlorhexidine-alcohol was shown to be superior to povidone-iodine in reducing SSIs, both superficial and deep.¹⁹ Chlorhexidine acts by disrupting cell membranes and carries a risk for ototoxicity. Povidone-iodine acts by oxidizing amino acids and disrupting cell membranes. Because iodine can produce hypothyroidism in low-birth-weight infants, its use should be limited accordingly.^{20,21} Alcohol acts by denaturing proteins. Iodine has the lowest risk for complications, and alcohol has the shortest duration of

action. Alcohol-based solutions should be avoided in neonates before of the possibility of burns.²² Chlorhexidine gluconate is recommended for use in children past the age of 2 months by the manufacturer for this reason.

4.1.2 Preoperative Medication Management

For elective neurosurgical patients, anticoagulation should nearly always be discontinued before surgery. Aspirin can be administered no more than 7 days before surgery without an adverse effect on coagulation, although aspirin may be intentionally continued through surgery in selected patients

Table 4.1 Common abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ADH	Antidiuretic hormone; vasopressin
AED	Antiepileptic drug
AVM	Arteriovenous malformation
CFU	Colony-forming unit
EEG	Electroencephalogram
EMLA	2.5% lidocaine, 2.5% prilocaine; dermal anesthetic
EVD	External ventricular drain
FFP	Fresh frozen plasma
ICP	Intracranial pressure
INR	International normalized ratio
IV	Intravenous
LR	Lactated Ringer solution
MAP	Mean arterial pressure
NPO	Nil per os ("nothing by mouth")
NS	Normal saline solution (0.9% sodium chloride)
OR	Operating room
PICU	Pediatric intensive care unit
PO	Per os ("by mouth")
PR	Per rectum
PRBCs	Packed red blood cells
PT	Prothrombin time
PTT	Partial thromboplastin time
SBP	Systolic blood pressure
SQ	Subcutaneous
SSI	Surgical site infection

(e.g., those with moyamoya). Nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen; medication dosages are listed in ► Table 4.2) should not be administered during the 24 hours before surgery. Patients on warfarin should be transitioned to heparin in the hospital with the consultation of the hematologist, or to low-molecular-weight heparin (enoxaparin [Lovenox] or dalteparin [Fragmin]) 3 days before the procedure. Low-molecular-weight heparin should be discontinued 24 hours before the procedure, and heparin 6 hours before the procedure. Clopidogrel (Plavix) must be stopped 5 to 7 days before surgery. The reason that the patient is taking the anticoagulant must be weighed against the risk for intraoperative and postoperative bleeding.

Antibiotics are administered within 1 hour of surgery for every case, with the possible exception of cases in which identification of a microorganism is desired. The usual choice of antibiotic is cefazolin, although clindamycin and vancomycin are second-line substitutes for those with a cephalosporin allergy. Antibiotic prophylaxis has been shown to be generally effective in reducing the risk for wound infection in a wide variety of adult cases.²³ Prophylactic antibiotic therapy has been shown to be effective for craniotomy and spinal surgery in adults, although no role for prophylaxis against gram-negative organisms or multiple doses of antibiotics could be proven effective.^{24,25} Prophylactic antibiotics reduce the risk for meningitis by approximately 50% in adult patients undergoing craniotomy.²⁶ A single dose has been shown to be adequate for surgical wound prophylaxis in many cases, including gastrointestinal surgery cases.²⁷ Repeat dosing while the patient remains in the OR is recommended to maintain adequate serum levels during surgery.²⁸ Studies have demonstrated the efficacy of intraoperative dosing of antibiotics in reducing postoperative incisional infections, although not postoperative meningitis.^{29,30} Additional dosing beyond the termination of surgery is not generally recommended.²⁸ However, the use of 24 hours of prophylactic antibiotics in patients undergoing implantation of shunts was found in a meta-analysis to reduce the rate of shunt infection.³¹ Dosing for more than 24 hours postoperatively in any case is not recommended.²⁸

The use of local anesthetic has several advantages. Long-lasting anesthetics like bupivacaine allow improved postoperative pain control, with a reduction in the need for opioid administration. The addition of epinephrine to the local anesthetic prolongs the duration of the anesthetic effect; it also produces vasoconstriction, thereby reducing blood loss during skin opening. This is especially desirable in neonates, in whom little blood loss is tolerated. The use of local anesthetic must be meticulously avoided in patients undergoing extracranial–intracranial bypass, to avoid both vasoconstriction and inadvertent injury to the donor vessel.

4.1.3 Infection Control Measures

Hand washing by surgical personnel is a variable process among institutions and individual surgeons. Chlorhexidine gluconate is clearly superior to povidone–iodine in terms of reducing the number of CFUs that surgical personnel have on their hands after performance of routine preoperative hand antisepsis. No effect of the length of time a scrub is performed has been demonstrated, although 2 minutes appears to be the minimum

necessary.³² Hand rubbing with an aqueous alcohol-based solution, preceded by a 1-minute nonantiseptic hand wash before the surgeon's first case of the day or when hands are overtly soiled, is as effective as traditional hand scrubbing with antiseptic soap in preventing SSIs.³³ The use of an alcohol-based chlorhexidine surgical rub (1% chlorhexidine gluconate and 61% ethyl alcohol w/w [Avagard; 3 M, St. Paul, MN]) instead of a traditional aqueous chlorhexidine scrub may be more effective in reducing the bacterial flora on the hands in both an immediate and a delayed fashion.³⁴ Multiple studies demonstrating a reduced number of CFUs on the hands with the use of chlorhexidine have been performed, but none has linked the use of any preoperative hand scrub or surgical site preparatory solution to a decreased incidence of SSIs.

Double gloving has been resisted by many surgeons because of reduced tactile sensation and increased cost. Nonetheless, bacterial migration through punctures in surgical gloves has been shown to occur.^{35,36} Double gloving has been shown to reduce the likelihood of blood-borne pathogen transmission, and some studies have suggested that it reduces the risk for SSIs.³⁷ This is a simple measure to reduce the incidence of infection for the patient and the surgical team and should be carried out routinely.

It has been suggested that the outer gloves be changed before shunt components are handled, and several studies have documented a decrease in the incidence of shunt infection when this is done.^{38,39} Bacteria are present on the outer gloves within 15 minutes of the initiation of surgery³⁸; changing the outer gloves after a period of time, or before handling implants, is reasonable. The use of a no-touch technique has been advocated by many pediatric neurosurgeons, but a recent study from the Hydrocephalus Clinical Research Network did not demonstrate a statistically significant decrease in infection when a no-touch technique was used.⁴⁰

Antibiotic-impregnated shunt catheters are available for use as external ventricular drains (EVDs) or ventriculoperitoneal shunts. The catheters are impregnated with rifampin and clindamycin (Bactiseal; DePuy, Warsaw, IN; Ares; Medtronic Neurosurgical, Goleta, CA) or with minocycline and rifampin (Ventriclear; Medtronic); no difference in infection rates has been identified between the two catheter types for external ventricular drains.⁴¹ One study of adult neurosurgical patients found that the use of antibiotic-impregnated EVDs was as effective as the use of systemic antibiotics in preventing cerebrospinal fluid (CSF) infection.⁴² Other studies have found a clear reduction in EVD infections with the use of antibiotic-impregnated catheters and have recommended their routine use.^{43,44} The use of prophylactic systemic antibiotics while an EVD is in place has been found to reduce the incidence of infection in multiple studies.⁴⁴ The use of antibiotic-impregnated shunt catheters may provide a reduction in shunt infection.³¹ A multicenter research initiative under way through the Hydrocephalus Clinical Research Network aims to identify factors that reliably decrease the incidence of shunt infections. The use of antibiotic-impregnated shunt catheters is one of the factors being investigated at present.

Skin closure is largely a matter of surgeon preference. Staples, nylon sutures, and absorbable sutures are options. There is a significant advantage to not having to remove sutures or staples in combative or fearful children. The use of staples may

Table 4.2 General dosing guidelines for common neurosurgical medications	
Drug	Dosing
Acetaminophen (Tylenol; McNeil, Fort Washington, PA)	PO/PR: Neonates: 10–15 mg/kg/dose every 6–8 hours Infants and children: 10–15 mg/kg/dose every 4–6 hours, maximum 3.25 g/day
Aspirin	PO: 3–10 mg/kg/day rounded to a convenient dose, maximum 325 mg/day
Bisacodyl (Dulcolax; Boehringer Ingelheim, Ridgefield, CT)	PO: Children 3–12 years: 5–10 mg/dose (0.3 mg/kg) Children ≥ 12 years: 10 mg/dose
Bupivacaine (Marcaine; Hospira, McPherson, KS)	SQ: 0.25% bupivacaine, 1:200,000 epinephrine; 1 mL/kg patient weight
Carbamazepine (Tegretol; Novartis, East Hanover, NJ)	PO: Initial: 10–20 mg/kg/day (up to 200 mg/day) divided into 2–3 times daily as tablets or 4 times daily as suspension; increase weekly by up to 100 mg/day until optimal response achieved; maximum 35 mg/kg/day or 1,000 mg/day Maintenance: divide into 3–4 doses
Cefazolin (Ancef; GlaxoSmithKline, Philadelphia, PA; Kefzol; Lilly, Indianapolis, IN)	IV: 15–25 mg/kg/dose; maximum 6 g/day
Clindamycin (Cleocin; Pfizer, New York, NY)	IV: 10 mg/kg preoperatively; maximum 600 mg/dose
Cyclobenzaprine (Flexeril; Janssen, Titusville, NJ)	PO: Children: dosage not established Adolescents: 5 mg 3 times daily, may increase to 7.5–10 mg/dose; use for more than 2–3 weeks not recommended
Dexamethasone (Decadron; Merck, Whitehouse Station, NJ)	IV/PO: Loading dose: 1–2 mg/kg/dose up to 10 mg/dose Maintenance: 1–1.5 mg/kg/day divided every 4–6 hours; maximum 16 mg/day; tapered off over 5 days
Diazepam (Valium; Genentech, South San Francisco, CA)	IV: 0.04–0.3 mg/kg/dose every 2–4 hours to a maximum of 0.6 mg/kg/8 h PO: 0.12–0.8 mg/kg/day divided every 6–8 hours, maximum 10 mg/dose
Dobutamine (Dobutrex; Lilly)	IV: 2–15 µg/kg/min continuous infusion, titrate to response; maximum 15 µg/kg/min
Docusate sodium (Colace; Purdue, Stamford, CT)	PO: 5 mg/kg/day divided into 1–4 doses, maximum 400 mg/day
Dopamine (Intropin; DuPont, Wilmington, DE)	IV: 1–20 µg/kg/min continuous infusion, maximum 50 µg/kg/min
Famotidine (Pepcid; Merck)	PO: Neonates and infants < 3 months: 0.5–1 mg/kg/dose every 24 hours IV: Neonates and infants < 3 months: 0.25–0.5 mg/kg/dose every 24 hours PO/IV: Children > 3 months: 0.5 mg/kg/dose twice daily, maximum 40 mg/day
Fentanyl	IV: Continuous analgesia: 1–2 µg/kg bolus, then 0.5–2 µg/kg/h, titrate to effect
Furosemide (Lasix; Sanofi, Bridgewater, NJ)	IV: Neonates: 1–2 mg/kg/dose every 12–24 hours Infants and children: 0.5–2 mg/kg/dose every 6–12 hours
Hydrocortisone (Cortef and Solu-Cortef; Pfizer)	IV stress dose for surgery: 50 mg/m ² bolus followed by 50 mg/m ² /day as continuous infusion for 48–72 hours IV stress dose for neonates: 20–30 mg/m ² /day divided into 2 or 3 doses IV stress dose in PICU: 2 mg/kg/dose x 1, then 2 mg/kg/day as a continuous infusion or divided every 6 hours PO physiologic replacement: Neonates: 7–9 mg/m ² /day divided every 8–12 hours Children: 0.5–0.75 mg/kg/day divided every 8 hours
Hydromorphone (Dilaudid; Purdue)	IV: 0.008 mg/kg/dose every 3 hours as needed, up to 0.015 mg/kg/dose
Ibuprofen (Advil, Pfizer; Motrin, McNeil)	PO: 4–10 mg/kg/dose every 6–8 hours, maximum 40 mg/kg/day or 3.2 g/day
Ketorolac (Toradol; Roche, Nutley, NJ)	IV: 0.5 mg/kg/dose every 6 hours up to 30 mg/dose; do not exceed use beyond 5 days
Labetalol (Normodyne; Schering, Kenilworth, NJ)	IV: 0.2–0.5 mg/kg/dose as frequently as every 10 minutes; maximum 20 mg/dose

Table 4.2 continued

Drug	Dosing
Levetiracetam (Keppra; UCB Pharma, Smyrna, GA)	IV/PO: 5–10 mg/kg/day divided into 2–3 doses, increased weekly to 60 mg/kg/day maximum; dose not established in children < 16 years although off-label use frequent
Mannitol (Osmitrol; Baxter, Deerfield, IL)	0.25–1 g/kg every 6 hours; maximum 50 g every 6 hours, maintaining serum osmolality at 310–320 mOsm/L
Metoclopramide (Reglan [injectable]; Baxter; Reglan [oral]; Alaven, Marietta, GA)	IV: 0.1–0.2 mg/kg/dose, repeated every 6–8 hours as needed; maximum 10 mg/dose
Morphine sulfate	IV: Neonates: 0.02–0.05 mg/kg/dose every 4–8 hours, maximum 0.2 mg/kg/dose Infants 0 to < 6 months: 0.02 mg/kg/dose every 4–6 hours, maximum 0.06 mg/kg/4 h Infants ≥ 6 months: 0.05 mg/kg/dose every 4–6 hours, maximum 0.12 mg/kg/4 h Children: 0.05 mg/kg/dose every 3 hours as needed, escalate to 0.15 mg/kg/dose as needed; maximum 15 mg/dose in children Adolescents (> 50 kg): 2.5–10 mg every 3 hours as needed PO: oral dose one-third as effective as IV dose
Naproxen (Aleve; Bayer, Pittsburgh, PA; Naprosyn; Roche)	PO: children > 2 years: 5–7 mg/kg/dose every 8–12 hours; maximum 1,000 mg/day
Nicardipine (Cardene; EKR Therapeutics, Bedminster, NJ)	IV: 0.5–1 µg/kg/min via continuous infusion, titrating to goal blood pressure with increases every 15–30 minutes; maximum dose 4–5 µg/kg/min
3% Normal saline	3–10 mL/kg as a bolus dose, or a continuous infusion beginning at 1 mL/kg/h and increased to effect, maintaining serum osmolality < 360 mOsm/L
Oxycodone (OxyIR; Roxicodone; Xanodyne, Newport, KY)	PO: 0.05–0.1 mg/kg/dose every 3 hours as needed; escalate as needed to 0.15 mg/kg/dose; begin at 5–10 mg/dose in adolescents > 50 kg
Phenobarbital	IV loading dose: 10–20 mg/kg; maximum 30–40 mg/kg IV/PO maintenance dose: Neonates: 3–4 mg/kg/day in 1–2 doses, increase to 5 mg/kg/day if needed Infants: 5–6 mg/kg/day in 1–2 doses Children 1–5 years: 6–8 mg/kg/day in 1–2 doses Children 5–12 years: 4–6 mg/kg/day in 1–2 doses Children > 12 years: 1–3 mg/kg/day in 2 doses
Phenytoin	IV: Loading dose: 15–20 mg/kg Maintenance dose: begin at 5 mg/kg/day divided into 3 doses, may increase to 10 mg/kg/day
Polyethylene glycol (MiraLax; MSD Consumer Care, Summit, NJ; GlycoLax; Kremers Urban, Seymour, IN)	PO: 0.5–1.5 g/kg/day, not to exceed 34 g/day; titrate to goal of two soft stools per day
Sucrose	
Vancomycin	IV: Children 1 month–12 years: 15 mg/kg/dose every 6 hours Children > 12 years: 15 mg/kg/dose every 8 hours; maximum 2,000 mg/dose

Note: All dosages should be confirmed with the hospital pharmacist before administration.

be associated with a lower risk for infection than the use of suture, but staples are also associated with increased pain.⁴⁵ Some surgeons apply an antibiotic ointment, such as bacitracin (X-Gen Pharmaceuticals, Big Flats, NY) or Neosporin (neomycin sulfate, polymyxin B, and bacitracin zinc; Johnson & Johnson, New Brunswick, NJ), over the suture line before applying a dressing. Others use petrolatum gauze (Xeroform; Covidien, Mansfield, MA). Dressings range from 2-octyl cyanoacrylate (Dermabond; Ethicon, Somerville, NJ), to Telfa (Kendall [Covidien]) secured with paper tape or a clear occlusive dressing (Tegaderm; 3M), to full head wraps with bandage roll, such

as Kerlix (Covidien) and Kling (Johnson & Johnson). Dressings are typically left in place for 24 to 48 hours. There is no advantage to leaving dressings in place longer, or in replacing them, over conventionally closed incisions. Some argue that dressings are unnecessary.^{46,47} The need to keep a child's hands away from the incision frequently mandates a dressing, however. The application of tissue adhesives, such as Dermabond, in addition to sutures may provide a lower risk for infection than suture or staples alone, although tissue adhesives should not be used independently for primary wound closure, as the risk of dehiscence is unacceptably high.^{48,49} One small study demonstrated

a lower rate of shunt infection with the use of subcuticular sutures and Dermbond than with conventional nonabsorbable skin sutures.⁵⁰

The use of antibiotic-coated suture has become popular over the last ten years. Triclosan-coated polyglactin 910 (Vicryl Plus, Ethicon) and poliglecaprone 25 with triclosan (Monocryl Plus, Ethicon) are the most popular choices. There are approximately as many studies concluding that the use of antibiotic-coated suture reduces the incidence of SSIs as there are that the use of antibiotic-coated suture has no impact on the incidence of SSIs.⁵¹⁻⁵⁴ The cost of antibiotic-coated suture is approximately 50% higher than the cost of standard suture,⁵⁵ so consideration of its use should not be taken lightly. The use of antimicrobial suture for wound closure resulted in lower infection rates in 61 patients undergoing 84 ventriculoperitoneal shunt surgeries in a prospective, randomized, double-blinded controlled trial.⁵⁶

4.1.4 Fluid and Electrolyte Management

Healthy children readily tolerate the absence of oral intake overnight. Standard preoperative instructions include nothing by mouth for 8 hours before surgery, with the following exceptions. Breast milk is allowed until 4 hours before surgery, and formula until 6 hours before surgery. Clear liquids, such as water, apple juice, Pedialyte (Abbott Nutrition; Columbus, OH), and Gatorade (Pepsico, Purchase, NY), are allowed until 2 hours before surgery. Medications normally taken in the morning are to be taken more than 2 hours before surgery with a sip of water. Certain medical conditions, such as moyamoya syndrome and diabetes insipidus, mandate that a patient be admitted to the hospital preoperatively for intravenous (IV) hydration overnight. These recommendations are based on the desire to limit both surgical and anesthetic complications associated with the procedure.

In general, hospitalized children beyond the neonatal period do best with 0.45% normal saline ($\frac{1}{2}$ NS) or more concentrated solutions, although there are reports of hyponatremia even with $\frac{1}{2}$ NS.⁵⁷⁻⁵⁹ Perioperative patients are more likely to develop hyponatremia than nonsurgical patients.⁶⁰ Neonates have higher water needs per kilogram and usually require D10 $\frac{1}{4}$ NS. Infants become dehydrated faster than older patients because of their higher body surface area. The use of isotonic fluids like NS or lactated Ringer solution (LR) is increasingly prevalent, as it avoids hyponatremia and prevents the hemolysis that results from hypotonic solutions. $\frac{1}{4}$ NS (osmolality 77) should not be administered peripherally, but D5 $\frac{1}{4}$ NS (osmolality 355) can be. Moderately hypertonic solutions are not problematic.

Daily maintenance IV fluid requirements are calculated as follows: 100 mL/kg for the first 10 kg, 50 mL/kg for the second 10 kg, and 20 mL/kg thereafter, with an upper limit of 2,400 mL/d. Sensible fluid losses, those that can be measured, including those from urine, stool, and nasogastric tube output, as well as surgical wounds, should be replaced. Insensible losses of water include water lost in perspiration and respiration, and these must be estimated. Exhaled air contains nearly 100% humidity. Maintenance fluids need to be adjusted for circumstances in which insensible losses (normally one-third of water loss) are increased, such as fever, the use of radiant warmers for premature infants (who may require 120 to 180 mL/kg/d), emesis or nasogastric suction, or the use of nonhumidified mechanical

ventilation. In general, the larger the incision, the larger the amount of intraoperative sensible fluid loss. And the smaller the patient, the larger the insensible losses because of the relatively large surface area of the skin.

The addition of dextrose to IV fluids is often avoided unless a patient's status is nothing by mouth (NPO) for a prolonged period of time or hypoglycemia (glucose < 70 mg/dL) is identified on blood testing. There is strong evidence that hyperglycemia increases the extent of infarction after stroke, so hyperglycemia is avoided to protect the vulnerable margins of a cortical resection. Hyperglycemia is also avoided for 24 to 48 hours following severe closed head injury, as several studies have demonstrated poorer outcomes in patients who were hyperglycemic on admission or during their hospitalization.^{61,62} Even a single dose of dexamethasone during the course of a craniotomy significantly elevates the serum glucose level and should be avoided in patients for whom hyperglycemia could be detrimental.⁶³

Hypoglycemia, however, particularly in neonates, entails its own set of problems and must be avoided as well. Whereas adults are able to maintain near-normal blood glucose levels for days, healthy neonates and young children become hypoglycemic after 24 to 48 hours. The glycogen stores of young children are adequate to maintain the serum glucose for no more than 5 to 10 hours. Because of the small muscle mass of children, oxidative metabolism of fatty acids occurs early, along with ketone body production. The relatively increased glucose requirements in children frequently result in hypoglycemia. The glucose in maintenance IV fluid is sufficient to provide approximately 20% of a patient's caloric needs, preventing ketoacidosis, but allows the loss of 0.5 to 1% of their weight each day. Neonatal hypoglycemia may be manifested by cyanosis, apnea, hypothermia, hypotonia, lethargy, or seizures. Consideration should be given to adding dextrose to IV fluid in neonates if enteral feeds are not expected to commence within 2 to 3 hours of surgery. Neonates require a glucose infusion rate of at least 6 to 8 mg/kg/min, which will usually be adequately supplied with a solution of D10 $\frac{1}{4}$ NS for term babies, with a goal serum glucose level above 60 mg/dL. Serum glucose levels should be closely monitored in patients who are NPO and not receiving dextrose in their IV fluids.

Intraoperatively, IV fluid management depends upon the goals of the surgery and estimated losses. Hyponatremia is meticulously avoided in all cases. Patients with brain tumors are maintained slightly hypovolemic, often with the assistance of mannitol, 3% NS, or furosemide (Lasix; Sanofi, Bridgewater, NJ), to minimize vasogenic edema of the tissue surrounding the tumor and to minimize the degree of retraction necessary to visualize and resect the tumor. In contrast, patients with moyamoya are aggressively hydrated, as their impaired cerebrovascular autoregulation limits their ability to adapt to hypovolemia without the risk for cerebral infarction. LR is routinely used as replacement for CSF in patients undergoing intraventricular endoscopy; this limits the incidence of mutism, which can develop postoperatively in these patients for reasons that are not understood.^{64,65} Patients enter the OR with a fluid deficit from being NPO for a number of hours before surgery. This is calculated as the maintenance IV fluid requirement multiplied by the number of hours the patient has been NPO, and the deficit is generally replaced in the first 2 to 3 hours of surgery. If the surgery lasts less than 2 hours, fluids can be replaced more rapidly and often are at the start of surgery because of relative

hypotension in the dehydrated patient, although rapid replacement of fluid can be very undesirable in patients undergoing craniotomy and must be discussed with the anesthesiologist before the start of the case.

Fluid replacement in the OR includes crystalloid, colloid, and blood products. The SAFE Study indicated that colloid replacement in patients with a disrupted blood–brain barrier (secondary to traumatic brain injury) was associated with higher mortality, so colloid (e.g., albumin) is almost never used in neurosurgical patients.⁶⁶ A neurosurgical patient's hemoglobin level is generally maintained at about 9 to 10 g/dL intraoperatively. Transfusion above a hemoglobin level of 8 g/dL has not been shown to lead to better outcomes, with the exception of patients with acute myocardial ischemia.⁶⁷ In selected patients with vascular or cardiac issues, transfusion at a higher hemoglobin level may be warranted.⁶⁸ The decision regarding intraoperative and postoperative transfusion should be based upon hemodynamic parameters (hypotension, tachycardia), and usually occurs at a hemoglobin concentration of 7 to 8 g/dL in patients without cardiac or central nervous system pathology.⁶⁸ A preoperative and intraoperative platelet count of 100,000/ μ L is necessary for hemostasis in neurosurgery, although much lower platelet counts are tolerated in general surgical patients (50,000/ μ L) and stable nonsurgical patients (10,000/ μ L).⁶⁹ Similarly, a prothrombin time (PT) of less than 16 seconds, an international normalized ratio (INR) of less than 1.2, and a partial thromboplastin time (PTT) of less than 39 seconds (depending on the norms at an individual institution) are necessary for intraoperative hemostasis, although values moderately outside of these limits do not produce bleeding difficulties in nonsurgical patients. The administration of fresh frozen plasma (FFP) has few guidelines but is generally recommended for patients with warfarin-related intracranial hemorrhage and for those undergoing massive transfusion.⁷⁰ Recent articles indicate that an INR of 1.5 (or possibly higher) does not produce increased bleeding in neurosurgical procedures, and that the administration of FFP produces fluid overload and an unnecessary delay in surgical intervention.⁷¹

A massive transfusion protocol has been established at the University of Pittsburgh for patients with major blood loss resulting from trauma or surgery (in whom the use of 10 units of packed red blood cells [PRBCs] is expected) in response to literature suggesting improved survival in patients transfused with high FFP- and platelet-to-red blood cell ratios.^{72–74} A pediatric massive transfusion protocol has been proposed, based on the same principles; triggers of persistent hemodynamic instability or ongoing bleeding after the infusion of 40 mL/kg of crystalloid are used to initiate the transfusion of PRBCs (30 mL/kg). The addition of FFP (20 mL/kg) is made after the loss of one blood volume, and the addition of platelets (20 mL/kg) and cryoprecipitate (4 mL/kg) after the loss of two blood volumes.⁷⁵ The off-label use of recombinant factor VII (Novoseven; Novo Nordisk, Plainsboro, NJ) can be considered in cases of continued blood loss.⁷⁵

4.2 Postoperative Management

4.2.1 Fluid and Electrolyte Management

Nearly all pediatric surgical patients (not only neurosurgical) are now placed on isotonic fluids (either NS or LR) in the

postoperative period.⁷⁶ It is clear that hypotonic maintenance IV fluids cause hyponatremia in children, with the potential for the development of hyponatremic encephalopathy, cerebral edema, and death in children who have severe infections or are in the postoperative state.⁷⁷ A trial in 258 postoperative patients revealed that hypotonic IV fluids (0.45% NS in this study) significantly increased the risk for hyponatremia compared with isotonic IV fluids (0.9% NS).⁷⁸ The development of hyponatremia is felt to be a function of the tonicity of the maintenance fluids, rather than of the volume of fluid administered.⁷⁹ Antidiuretic hormone (ADH) levels are normally elevated in the 24 hours following surgery, and fluid restriction delays the normalization of ADH levels.⁸⁰ Sodium losses from an EVD can warrant replacement if hyponatremia develops. Postoperatively, it is common for neurosurgical patients to be placed on NS.

Sodium levels are strictly maintained at the upper limit of normal or higher (140 to 150 mEq/L is a fairly standard range) in the majority of pediatric neurosurgical patients. The blood–brain barrier is often disrupted at least locally in these patients, allowing the passive diffusion of water into the brain and a corresponding increase in cerebral edema and intracranial pressure. The blood–brain barrier comprises tight junctions between the endothelial cells lining the capillaries of the brain; the astrocytic foot processes surrounding the capillaries may play a minor role as well. The blood–brain barrier is disrupted by prematurity, infection, ischemia and stroke, neoplasia, hypertension exceeding the limits of autoregulation, and trauma (including surgery).⁸¹ It can be intentionally disrupted with the use of hyperosmolar solutions, such as mannitol, to improve the delivery of chemotherapeutics. Increasing the sodium level in the bloodstream decreases the amount of free water in the brain, both intracellularly and extracellularly. The IV use of hypertonic saline or mannitol exerts an osmotic pressure gradient across the blood–brain barrier, allowing water to diffuse down the osmotic pressure gradient into the bloodstream. When the blood–brain barrier is disrupted, these molecules freely enter the brain through the widened tight junctions, leading to edema, excitotoxicity secondary to the accumulation of excitatory amino acids, and the loss of cerebral autoregulation. Steroids and hypothermia are thought to reduce the permeability of the blood–brain barrier.

Hypertonic saline at various concentrations, with 3% NS the most common (a bolus dose of 3 to 10 mL/kg or a continuous infusion beginning at 1 mL/kg/h and increased to effect), is used as a treatment for intracranial pressure (ICP) above 20 mm Hg in pediatric traumatic brain injury, titrated to an ICP below 20 mm Hg and a serum osmolality below 360 mOsm/L.⁸² Mannitol is also frequently used, although clinical studies demonstrating its efficacy are lacking.⁸² Doses of 1 g/kg reduce ICP through a reduction in blood viscosity in the short term (less than 75 minutes) and through an osmotic effect lasting up to 6 hours. This effect requires an intact blood–brain barrier; mannitol may diffuse into injured areas of the brain, pulling free water into the parenchyma.^{83,84} 3% NS functions via similar mechanisms, although much higher serum osmolality is tolerated by patients given 3% NS than by those given mannitol.⁸⁵ 3% NS is also useful in treating cerebral salt wasting.

4.2.2 Perioperative Medications

Antiepileptic drugs (AEDs) are often administered prophylactically in the perioperative period. The risk for postoperative epilepsy ranges from 12 to 17%.^{86,87} The administration of phenytoin in the perioperative period was shown to reduce the chances of postoperative epilepsy from 17 to 8% in a double-blinded trial of 203 patients undergoing craniotomy.⁸⁸ The chances of perioperative seizure can be increased (sevoflurane, enflurane) or decreased (thiopental, halothane) by the use of certain anesthetics.⁸⁹ A seizure can be induced in a patient with epilepsy by using anesthetics that are not proconvulsant in the normal brain (e.g., ketamine, isoflurane).⁸⁹ The same anesthetic drug can be proconvulsant or anticonvulsant, depending on the clinical setting and dose.⁹⁰ Risk factors for perioperative seizures include a supratentorial tumor, age younger than 2 years, and hyponatremia due to inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting.⁹¹ Nonaccidental trauma, prehospital hypoxia, a Glasgow Coma Scale score of less than 8, and subdural hematoma have also been identified as risk factors for seizure in trauma patients.^{92,93}

AEDs decrease the early (<7 days) but not the late (>7 days) risk for seizure after head injury in adults.^{82,94,95} Studies have principally been performed with phenytoin, although carbamazepine and phenobarbital have also been shown to provide a reduction in early posttraumatic seizures.⁹⁵ The combination of phenytoin and phenobarbital appears to be the most effective in reducing provoked seizures; the majority of drugs developed after 1980 have not been tested.⁹⁶ Levetiracetam and phenytoin are both associated with a low risk for early postoperative seizures, and levetiracetam is associated with fewer early adverse reactions.⁹⁷ Some small studies of levetiracetam suggest equivalent seizure control and improved neurologic outcomes, but the numbers do not reach statistical significance, and this fact combined with the 20-fold higher cost of levetiracetam suggest that these data be interpreted with caution.^{98–100} Because of the higher rate of side effects with phenytoin, a common practice is to begin a patient on phenytoin perioperatively and switch to levetiracetam if any side effects occur. This transition has been shown to be safe in a small pilot study.¹⁰¹ Several small studies not reaching statistical significance failed to show a reduction in early posttraumatic seizures for phenytoin in children.¹⁰² No drug has been shown to reduce the incidence of late seizures following trauma or craniotomy. The effect on children is extrapolated to be the same as for adults, but confirming data do not exist.

The use of AEDs in children following head trauma and craniotomy for other reasons is controversial, and largely a matter of surgeon preference. A common management choice is to load a patient who has a tumor or vascular malformation with an AED at the start of surgery and continue the AED for some period of time thereafter. Although the literature does not support a role for AEDs in preventing late-onset epilepsy, it is certainly not ideal for the recovering brain, unfused craniotomy bone, and healing skin to be subjected to the trauma and hypertension associated with a generalized tonic-clonic seizure. Many pediatric neurosurgeons advocate 6 to 12 weeks of AED therapy after a craniotomy for this reason and taper the drug after that time point, with or without an electroencephalogram (EEG) before or after completion of the taper.

The routine use of perioperative dexamethasone to limit peritumoral cerebral edema was initiated in the 1960s.¹⁰³ The use of dexamethasone has expanded over the years, and it is now used by some surgeons for patients undergoing surgery for aneurysms or arteriovenous malformations, surgery for Chiari malformations, craniofacial surgery, or resection of epileptic foci, in addition to those with brain tumors. Dexamethasone, although accompanied by a host of side effects, including mood changes, increased oral intake, and acne, in addition to the classic cushingoid appearance (buffalo hump, moon facies, abdominal striae), produces an improvement in the neurologic examination findings in some patients, a reduction in nausea and vomiting, improved pain control, and a shortened hospital stay.^{104–106} Dexamethasone dosing if continued for 5 days must not be abruptly discontinued, to prevent acute adrenal insufficiency; rather, it must be tapered off over a minimum of 5 days, with the rate of recovery dependent upon the length of steroid administration.¹⁰⁷ Dexamethasone is a strong glucocorticoid agonist with little to no mineralocorticoid effect, whereas hydrocortisone is a stronger mineralocorticoid agonist than glucocorticoid agonist. Hydrocortisone is thus administered preferentially to patients who have primary or secondary adrenal insufficiency; a classic example is the patient with a craniopharyngioma. Stress dosing should be undertaken for surgery, illness, and fever in patients with panhypopituitarism or adrenal insufficiency.¹⁰⁸ Stress dosing is roughly three times the maintenance dose. The necessity of stress dosing has been questioned in many patients on long-term glucocorticoids, but not for neurosurgical patients; a patient receiving high-dose dexamethasone for cerebral edema does not require the additional administration of hydrocortisone.¹⁰⁸

A course of dexamethasone is highly effective in treating chemical, or aseptic, meningitis following a craniotomy. The secondary hydrocephalus often resolves after the first few days of a several-week tapering course of dexamethasone. These patients typically present with a fever and meningismus but are alert and interactive, whereas patients with bacterial meningitis are usually somnolent. Once infection has been ruled out with a lumbar puncture demonstrating the absence of bacteria and a lymphocytic predominance, a weight-dependent bolus of dexamethasone followed by regular dosing of a slowly tapering course over several weeks produces resolution of symptoms.

Blood pressure management is important, and often critical, in postoperative neurosurgical patients. Patients who have undergone craniotomies for tumor or epilepsy focus resection are predisposed to hemorrhage if allowed to become hypertensive. An upper limit is usually set for the systolic blood pressure (SBP), as intermittent spikes in blood pressure can be reasoned to override tenuous clot formation in, or coagulation of, a blood vessel, eliciting a significant intracranial hemorrhage; upper and lower limits for mean arterial pressures (MAPs) are also typically specified to ensure adequate perfusion of the brain while limiting venous ooze into the resection cavity. Blood pressure and heart rate norms vary with patient age and size, and intra- and postoperative targets should be adjusted accordingly. A general rule for adult patients is to keep the SBP under 140 to 160 mm Hg; in children, the baseline preoperative blood pressure is a good approximation of the goal postoperative blood pressure. β -Blockers (propranolol, metoprolol) reduce cardiac output by reducing contractility and the heart

rate. α -Blockers (prazosin, doxazosin) reduce afterload. Mixed α -/ β -antagonists (labetalol, carvedilol) may also be used. Calcium channel blockers (nicardipine, nifedipine, verapamil, diltiazem) reduce systemic vascular resistance with minimal effect on contractility. Nimodipine, a calcium channel blocker commonly used for adult patients with aneurysms to reduce the complications of vasospasm, may be used in children to treat or prevent vasospasm. However, the dose and efficacy of this strategy in children have not been established, and children seem to have many fewer complications of vasospasm (behavioral change, stroke) than do adults following aneurysmal subarachnoid hemorrhage.^{109,110} Angiotensin-converting enzyme (ACE) inhibitors (captopril, lisinopril) produce vasodilation by reducing the body's production of angiotensin, but they have prolonged durations of action and effects on renal function that limit their usefulness. Vasodilators (hydralazine, minoxidil) are also used for hypertensive control. Nitroprusside causes vasodilation as a nitric oxide donor to the vasculature, reducing afterload, without an effect on contractility. Although its short half-life allows rapid dose titration, the production of cyanide during its metabolism yields significant toxic potential. Nitroprusside may increase ICP by increasing cerebral venous blood volume and should be administered only as a drug of last resort, together with thiosulfate. β -Blockers and calcium channel blockers, particularly labetalol and nicardipine, are the antihypertensives most commonly used in the PICU for neurosurgical patients.

Hypotension, relative or absolute, may be equally harmful. Patients who have undergone AVM resection may develop normal perfusion pressure breakthrough (cerebral edema or hemorrhage, thought to be from altered cerebral autoregulation secondary to the restoration of normal blood flow to the chronically ischemic tissue surrounding the AVM) if allowed to achieve normotension.¹¹¹ Such patients should routinely be maintained at least at the lower limit of cerebral perfusion to reduce the chances of this dangerous syndrome developing. Patients with moyamoya syndrome and resultant altered cerebral autoregulation may have strokes at higher than anticipated cerebral perfusion pressure.¹¹² Patients in spinal shock may require augmentation of their blood pressure, as volume resuscitation is contraindicated in these patients. Selected patients may require the use of pressors to increase the MAP. Epinephrine and dopamine are β -receptor agonists at low doses and α -receptor agonists at high doses. Epinephrine has a narrow therapeutic range and carries a significant risk for adverse reactions; it is used principally for cardiac arrest and anaphylaxis. Low-dose dopamine (0.5 to 5 $\mu\text{g}/\text{kg}/\text{min}$) increases renal and cerebral blood flow. Intermediate-dose dopamine (5 to 15 $\mu\text{g}/\text{kg}/\text{min}$) increases cardiac output. High-dose dopamine (> 15 $\mu\text{g}/\text{kg}/\text{min}$) produces progressive systemic and pulmonary vasoconstriction, increasing afterload and limiting cardiac output. Dobutamine is principally a β_1 -agonist (increased cardiac output), although it has mild β_2 effects (vasodilation). Norepinephrine is an α -receptor agonist that increases systemic vascular resistance through diffuse vasoconstriction, an effect that overshadows its minor effect on cardiac output. This is a second-line drug used principally in septic shock. Dopamine and dobutamine are the drugs of choice for increasing MAPs in the PICU.

Nausea and vomiting are common side effects of general anesthesia, and their incidence is increased in children.¹¹³ Nausea is partially controlled by the frequent use of intra- and postoperative dexamethasone and histamine₂-blockers (such as famotidine and ranitidine) in neurosurgical patients. Anesthesiologists routinely administer at least one antiemetic drug during surgery. The drug of choice for prophylaxis and treatment is a serotonin (5-HT₃) antagonist, such as ondansetron (Zofran; GlaxoSmithKline, Philadelphia, PA). Antiemetics like metoclopramide (Reglan), prochlorperazine (Compazine; GlaxoSmithKline), and promethazine (Phenergan; Baxter, Deerfield, IL) have potential neurologic and respiratory side effects and should be used as second-line agents and with caution.

Constipation is exceedingly common postoperatively in pediatric patients. This is problematic, as Valsalva maneuvers increase the risk for pseudomeningocele formation and CSF leak. Constipation causes unnecessary pain for the postoperative patient and can needlessly prolong a hospital stay. Patients should be routinely started on an osmotic laxative, such as polyethylene glycol (MiraLax; MSD Consumer Care, Summit, NJ), which is extremely well tolerated by patients, as soon as they begin an oral diet. An emollient stool softener, such as docusate (Colace; Purdue, Stamford, CT), or stimulants, such as senna (Senekot; Purdue) and bisacodyl (Dulcolax; Boehringer Ingelheim, Ridgefield, CT), are more objectionable to pediatric patients because of their taste but are adequate alternatives. Enemas and suppositories are less often necessary when these medications are begun early in a patient's hospital course.

4.2.3 Pain Management

Pain control in surgical patients is a critically important issue. The accurate assessment of pediatric pain is an essential part of postoperative management, as it allows the prevention of both over- and underadministration of pain medication. Many institutions have developed a pediatric pain management service to assist practitioners with this management. The most commonly used scales are CRIES for neonates, the Wong-Baker FACES scale for toddlers, FLACC (*face, legs, activity, cry, consolability*) for slightly older children, and VAS (visual analog scale) in children older than 7 years.¹¹⁴⁻¹¹⁹ The administration of local anesthetic, either a long-acting medication (such as bupivacaine) at the start of surgery or a shorter-acting medication (such as lidocaine) at the end of surgery, is effective in providing several hours of postoperative craniotomy pain control.¹²⁰ Oral sucrose may be helpful in minimizing distress for neonates past 34 weeks of gestation. The usual dose is 0.5 to 1.5 mL of 24% sucrose, given by syringe 2 minutes before the procedure. Breast milk and glucose are reported to be equally effective. Swaddling and nonnutritive sucking are first-line pain-relieving measures in neonates and infants. Acetaminophen and ibuprofen are typically administered in preference to oral opioids. Many patients require only acetaminophen or ibuprofen after a proximal ventriculoperitoneal shunt revision. Several studies have suggested that ibuprofen provides better pain relief than codeine or acetaminophen with codeine in children with long bone fractures.^{121,122} Topical skin anesthetics, such as EMLA and amethocaine gel, should be considered before painful procedures like IV placement, lumbar puncture, or suturing in infants

and children when possible, to minimize the pain and distress associated with the procedure.¹²³

Opioid administration is common, although the topic is controversial. Many neurosurgeons limit opioid administration in their postoperative patients because of a concern that somnolence or vomiting from postoperative cerebral edema or hemorrhage could be dismissed as a medication side effect. Opioids are to be administered in a response-dependent manner. Side effects like respiratory depression and somnolence occur after pain control has been achieved, so opioids should not be withheld for pain control because of a fear of these side effects. The most commonly used IV medication is morphine; hydromorphone (Dilaudid; Purdue) is occasionally used as a second-line drug in patients whose pain is refractory. The use of IV opioids should always be considered in neonates, in whom oral opiates are not recommended, although acetaminophen is highly effective in these patients. A morphine dose of 0.02 to 0.05 mg/kg IV every 4 to 8 hours may be used with caution in neonates, with close monitoring for respiratory depression, as pharmacokinetics in this age group are variable.¹²⁴ Morphine metabolism is decreased in infants younger than 6 months of age, and infants correspondingly require lower doses of morphine for pain control.¹²⁵ When older patients begin tolerating an oral diet, the IV opioid is typically transitioned to an oral opioid like oxycodone or hydrocodone. These drugs are favored over codeine because they provide more consistent analgesia. Oral morphine is three times less potent than IV morphine, and dosing must be adjusted accordingly.¹²⁶ Pediatric patients are likely to develop symptoms of opioid withdrawal after as little as 5 days of fentanyl infusion and may require transition to a tapering dose of methadone.¹²⁷

Patient-controlled analgesia (PCA), although infrequently used in young children, provides superior pain control in children older than 5 years of age.¹²⁸ PCA by proxy (parental administration of opioid) has been shown to have an increased incidence of respiratory depression secondary to opioid overdose, and it must be used with caution and extensive education of the proxy user.¹²⁹ Medications like low-dose ketamine (a dissociative anesthetic) can be added to the PCA for improved pain control and decreased opioid administration. Epidural PCA is used in patients undergoing spinal surgery, although rarely in patients undergoing craniotomy. A continuous epidural morphine infusion, with or without bupivacaine, has been demonstrated to be highly effective in patients undergoing lumbar dorsal rhizotomy.¹³⁰ Meta-analyses have demonstrated that continuous epidural analgesia is more effective in controlling postoperative pain than IV opioids (via either PCA or intermittent administration).^{131,132} Patients having spinal surgery, to include posterior fossa surgery, frequently experience spasm in the paraspinal musculature. This responds well to the administration of diazepam (Valium) or cyclobenzaprine (Flexeril). These drugs have a sedating effect and must be administered with caution.

The use of IV ketorolac (Toradol; Roche, Nutley, NJ) has been controversial in neurosurgery. Many neurosurgeons are reluctant to use it because of a concern about postoperative hemorrhage. Reports exist in the literature describing the development of spinal epidural hematomas in patients on ketorolac. One such case report describes an elderly patient who developed a spinal epidural hematoma after a lumbar puncture

while on enoxaparin, aspirin, and ketorolac.¹³³ No reports of intracranial hemorrhage in patients receiving ketorolac exist in the literature to date. A study of 89 adult patients undergoing lumbar microdiscectomy demonstrated improved pain control and no increased bleeding (from surgical wound or by coagulation parameters) with a single dose of ketorolac administered at the termination of surgery.¹³⁴ Multiple studies have confirmed the absence of an increased risk for postsurgical bleeding with the use of ketorolac in children, with the possible exception of those undergoing tonsillectomy.¹³⁵ Ketorolac is not recommended for use in children younger than 1 year of age, although it is routinely used at Children's Hospital of Pittsburgh in infants who have subgaleal drains in place. An increased risk for bleeding has been demonstrated in infants younger than 21 days of age.¹³⁶ Ketorolac is routinely used at Children's Hospital of Pittsburgh in the postoperative setting, particularly for pain control in patients undergoing Chiari decompressions or craniostomy repair, starting as soon as immediately postoperatively. Some surgeons opt to begin therapy with ketorolac a day or two following surgery, if clinically warranted.

An additional concern centers on conflicting reports in the literature suggesting that the use of nonsteroidal anti-inflammatory medications may inhibit spinal fusion. An increased rate of pseudarthrosis is well reported in adults.¹³⁷⁻¹³⁹ More recent literature has indicated that the short-term use of ketorolac (48 hours postoperatively) has no effect on spinal fusion.¹⁴⁰ A predisposition to pseudarthrosis or nonunion has not been demonstrated in children following instrumentation for scoliosis.¹⁴¹ Ketorolac produces superior pain control with fewer side effects than opioids, and although the risks must be weighed, its use is highly effective in many patients.

4.2.4 Restriction of Activity

Activity restrictions are imposed regularly for pediatric neurosurgical patients. Little evidence exists, however, to guide these decisions. Only the results of practice surveys completed by practicing pediatric neurosurgeons exist for most clinical questions. Return to school or day care is an important consideration. Children are kept out of crowded situations like school or day care because of concerns regarding possible injury to the incision, pain production, bleeding into a resection cavity, infection, and possibly the management of new neurologic deficits. Most children are able to return to school or day care within 2 weeks of a craniotomy. Pain and limited mobility may prevent patients undergoing spinal surgery from returning to school for 4 to 6 weeks. Older children may need to remain out of school for a longer period of time and undergo home tutoring so that they will be at the same level academically as their peers when they return to the classroom. Most school districts are mandated to provide a home tutor for any patient deemed by a physician to be unable to return to school for 4 weeks.

It is logical that Valsalva maneuvers should be limited following intradural spinal or posterior fossa surgery for a period of time following surgery, to minimize pseudomeningocele formation or CSF leak. This author has not observed pseudomeningocele formation more than 6 weeks postoperatively and uses this time period to instruct families to limit Valsalva maneuvers. Patients are restricted from lifting more than 5 pounds, straining, and physical activity beyond walking during this time. Patients

are placed on stool softeners to limit constipation. Following the 6 weeks, these restrictions are lifted completely for the majority of patients. Patients who have undergone Chiari decompression undergo a slower mobilization regimen, with running and swimming permitted after 6 weeks and noncontact competitive sports permitted after 3 to 6 months, depending upon the patient and the sport. Return to gym class depends upon the patient's neurologic deficits and typically occurs at least 4 to 6 weeks following return to school.

Return to sports is a particularly urgent issue for many families. Cranial concerns include the strength of the fusion between the craniotomy bone and the skull, the risk for hemorrhage associated with neovascularization and scar tissue, and risks for CSF dynamic alteration.¹⁴² While return to sports following concussion has been widely discussed and multiple sets of guidelines exist, return to sports following craniotomy has not been studied in a systematic way. Current guidelines for sports-related concussion advise against return to play in patients with neurologic symptoms, with or without provocative testing.¹⁴³ This guideline should certainly be observed in patients recovering from a craniotomy. Any patient with permanent central neurologic deficits should be prohibited from a return to contact sports.¹⁴² Most neurosurgeons insist that computed tomography of the head demonstrate fusion of the craniotomy bone before an athlete is permitted to return to play.¹⁴⁴ Patients undergoing posterior fossa surgery should be counseled about the potential decrease in ligamentous stability at the craniocervical junction as a result of the surgical approach.

Return to sports following spinal injury or surgery is problematic, as well. Several issues make the pediatric spine more vulnerable to injury than the adult spine. The pediatric head is larger relative to the body than is the adult head, allowing increased momentum with rapid movement. The pediatric paraspinal muscle mass is relatively less well developed, smaller, and more flexible than that of the adult, rendering it less able to withstand significant forces. The ligaments of the pediatric spine are more flexible than those of the adult, allowing more movement within the vertebral column and resultant spinal cord injury, without an identifiable ligamentous injury. This mobility, combined with the frequent finding of cervical spinal stenosis, is thought to be responsible for the "stinger" phenomenon seen commonly in high school football players. A stable spine by established criteria (normal strength, full range of motion without pain, and the absence of compressive forces) is a baseline requirement for return to play. Patients who have undergone spinal fusion are prohibited from collision sports on a permanent basis by the majority of spinal surgeons, from contact sports by some, and from noncontact sports (golf, swimming) for a variable period of months following surgery.¹⁴⁵ The decision regarding return to play must be made by the neurosurgeon and parents in conjunction, as only the family can determine their level of risk aversion.

Restriction of unoperated patients from activity is controversial. Because of case reports in the literature regarding subdural hematoma formation following participation in sports, including basketball, soccer, and football, in patients with arachnoid cysts, counseling of the parents regarding the risks associated with contact sports is held.¹⁴⁶⁻¹⁴⁸ Both arachnoid cysts and asymptomatic Chiari malformations are viewed as relative contraindications to participation in contact sports.¹⁴²

Many pediatric neurosurgeons restrict patients with ventriculoperitoneal shunts from participating in contact sports, although the established risk for complications (including shunt disconnection and subdural hematoma formation) is well under 1%.¹⁴⁹ With little information in the literature to inform decision making, counseling of the family regarding the potentially serious consequences must be undertaken in these cases.

4.3 Conclusion

A final topic, critical to the care of the pediatric neurosurgical patient, is the relationship between the neurosurgeon and the parents of the patient. The parents have been placed in the excruciating role of trusting a relative stranger to cut open their child's body, fix a problem, and return the child to them in the same or better condition. They must acknowledge their inability to protect their child from the hardships of life, and even from the pain of surgery. They feel helpless and desperate. The stress for some families is intolerable. Extensive discussion of the risks and benefits of surgery, as well as the likely outcome, lessens the burden somewhat. We in pediatric neurosurgery frequently see families at the most stressful moments of their lives, and we must deal with them with the utmost sensitivity.

Pearls

- Chlorhexidine gluconate produces the greatest reduction in CFUs on a surgeon's hands after a surgical scrub or on a patient's skin after a preoperative preparation; one study has linked chlorhexidine skin preparation to a decreased rate of SSIs.
- Hyponatremia must be avoided in all hospitalized children, not only those undergoing craniotomies. The administration of hypotonic IV fluids is associated with hemolysis, cerebral edema, and death in children.
- The development of hyper- or hypoglycemia is also problematic, and the serum glucose must be meticulously monitored when a patient's status is NPO and the patient is not receiving dextrose in his or her IV fluids.
- Massive transfusion protocols have been developed for patients in whom a large surgical or traumatic blood loss is expected, as survival appears to be improved in patients transfused with high FFP- and platelet-to-red blood cell ratios.
- The use of ketorolac for pain control, although the risks must be weighed, is associated with superior pain control and decreased side effects relative to the use of opioids.
- Although one goal of surgery is to return the patient to his or her prior level of function, the return to sports is a highly individualized decision that must be made in conjunction with the patient's family.

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5 Pediatric Neurosurgery in Developing Countries

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Many physicians who have worked in developing countries, even for a brief time, have been impressed by the great numbers of children who present with advanced stages of hydrocephalus (HC) and other diseases (► Fig. 5.1). The most commonly encountered condition is infant HC, which if untreated leads to death by the age of 2 years in 50% of cases and to significant disability in the majority of survivors; nonetheless, most children with HC in sub-Saharan Africa (SSA) go untreated. The reasons are multiple, but one reason is the lack of neurosurgeons in the region. There are around 100 neurosurgeons spread across SSA.¹ If all infants with hydrocephalus had access to care in the centers where these neurosurgeons practice, the average annual case load for a neurosurgeon would be at least 1,000 operations per year if infant HC were all he or she treated, not counting additional operations for shunt failure and infection—clearly an untenable situation. In addition, families typically have very limited means for travel, and in regions with poor infrastructure or security concerns, travel can be dangerous as well as difficult.

Before being brought to a medical center, many children are taken to a “practitioner of traditional medicine,” who may treat them with herbs or with focal cautery in the region of the abnormality (► Fig. 5.2). Families able to access a center with neurosurgical capabilities may be frustrated by their inability to pay for the cost of treatment, which typically includes purchasing a shunt. Because the cost of even a baseline shunt is prohibitive for many families, some surgeons insert either a length of Silastic tubing, tying off the distal end and making cuts just about the tie to create “slit valves,” or insert a valveless infant feeding tube. Such shunts are economical and considered by some to be effective, particularly in treating postinfectious HC.

A further obstacle to treatment in these children is a lack of general awareness in regard to the nature of hydrocephalus and the fact that it is a treatable condition. In areas where HC treatment has not been previously available, the public should be made aware of the condition of infant HC, what it looks like,

and where to get help. Depending upon the local culture, it may be appropriate to emphasize that this is a treatable medical condition, not the result of spiritual forces. Experience in Uganda demonstrated that this may be done effectively through newspaper and radio informational announcements, the result of which was a gradual decline in the age and disease severity of patients presenting for treatment over several years.

This speaks not only to the burden of disease, but also to the lack of access to diagnosis and treatment. In SSA, the annual number of new cases of infant HC can be minimally estimated to be more than 90,000, and potentially more than 300,000.² We recently reported that, after the use of a mortality-adjusted minimal estimate of annual cases of infant HC in SSA (82,000), the annual economic burden is at least 1 billion U.S. dollars, and possibly as much as to 56 billion U.S. dollars (depending upon the economic methods employed).² In the same study, we demonstrated that the most conservative estimate of the benefit-to-cost ratio for treating HC is 7:1, with an upper bound estimate of 50:1.

5.1 Congenital Lesions

5.1.1 Hydrocephalus

The most common cause of infant HC throughout SSA is unknown, and the causes may vary regionally or have differences in referral patterns. A previous report suggested congenital causes of HC to be most common.⁴ At CURE Children’s Hospital of Uganda (CCHU), we found ventriculitis to be the most common cause of infant HC, accounting for 60% of the cases, with three-quarters of the infections occurring within the first month of life as a component of neonatal sepsis.⁵ We have presented evidence suggesting that *Acinetobacter* and related species may be the dominant infectious agents.⁶ This is in



Fig. 5.1 A 7-month-old child who presented with untreated occipital encephalocele and thoracic myelomeningocele.



Fig. 5.2 Thoracolumbar scars resulting from the treatment of back pain secondary to a spinal-intraspinal tuberculoma by a practitioner of traditional medicine.

contradistinction to neonatal sepsis and meningitis in developed countries, where group B streptococci and *Escherichia coli* predominate. We have also demonstrated that in Uganda, infection peaks are tightly linked to rainfall patterns.⁷ Similarly, at Kijabe Hospital in Kenya, the most common etiology of HC was reported to be prior infection among all patients older than 3 months; however, for those younger than 3 months at treatment, myelomeningocele was the more common etiology.⁸ Thus, it is possible that many cases of infant HC in this region might ultimately be avoided. Public health strategies for the effective prevention and treatment of neonatal sepsis are sorely needed.

Clinical Presentation

Whether postinfectious or associated with spina bifida, HC is most common in infants, who may present with head circumferences ranging from normal to more than 60 cm, and it is accompanied by the same symptoms and signs that are seen in developed countries. Infants are often anemic and malnourished, and they have higher risks for infection and poor wound healing after shunting. Computed tomography (CT) and magnetic resonance (MR) imaging are available in few centers; ultrasonography is more widely available. Ultrasound images permit measurements of the lateral and third ventricles; the fourth ventricle is seen less commonly unless it is grossly abnormal.

The ethical issue of whether to treat severe infantile HC is a recurring one. Infants who are not treated develop progressive macrocephaly, sometimes to head circumferences of 80 cm, and many die of aspiration pneumonia or malnutrition within 2 years. However, some infants live for several years, and their caregiver burden is enormous. Insertion of a ventriculoperitoneal (VP) shunt or treatment with endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC) may have no benefit on the neurologic condition of some infants with severe HC, but the prevention of severe macrocephaly has considerable benefit for the caregivers—not only because of the reduced weight of the infant head but also because of fewer pressure ulcers in the parietal regions.

Medical Treatment

At times, the treatment of severe HC is futile. If insertion of a VP shunt is thought to carry unacceptable morbidity because of malnutrition, poor home environment, or ventriculitis, and if cerebrospinal fluid (CSF) production cannot be diminished by CPC, medical treatment with acetazolamide may be considered. Doses of 50 mg/kg per day have been reported to significantly diminish CSF production for up to 1 month; the longer-term effects are unknown.⁸

Treatment with Shunts

In the best of circumstances, shunts are expected to fail at least once in the first few years after placement. In the North American Shunt Design Trial, 61% of patients were free of shunt failure at 1 year and 47% at 2 years, with a shunt infection rate of 8.1%.⁹ Even though some have reported higher shunt complication rates for SSA,¹⁰ others have reported outcomes comparable to those in North America. In a prospective study of 195

consecutive children at CCHU with 90.3% 1-year follow-up, 54.5% of patients survived to 1 year with no shunt complications (including infection, wound complication, and shunt malfunction), with all shunt malfunctions occurring within the first 3 months.¹¹ In that study, the shunt infection rate in the first year was 9.7%. A subsequent survival analysis of 900 first-time shunt placements at CCHU demonstrated the infection rates at 30 days, 90 days, 6 months, 1 year, and 2 years to be 5.7%, 9.5%, 11.7%, 13.3%, and 15.2%, respectively.¹⁶ It was notable that although the majority of known infections occurred in the first 6 months, late shunt infections continued to occur over the 7-year time span of the study at a rate of about 1% per year. A *retrospective* analysis of 574 patients at Kijabe Hospital in Kenya, with a mean follow-up of 8.9 months in 76% of patients, demonstrated that 65% had no shunt complications within the first 2 years, and shunt infection was diagnosed in 9.1%.⁶ However, *prospectively* collected data in Kijabe indicate a current infection rate of 15 to 20%. In both of these institutions, the shunt predominantly used was the inexpensive Chhabra shunt, for which no difference was found, in regard to rates of shunt failure or infection in the first year, when it was compared in a randomized prospective trial with a shunt commonly used in North America that costs 20 times more.¹¹ Thus, it is encouraging that even when a very inexpensive shunt system is used, the expected outcome for shunt treatment in SSA may not be substantially different from that in more developed countries. Higher shunt complication rates would be expected because of previously cited factors, such as malnutrition, thin skin, anemia, and concurrent illnesses.

Ventriculoscopic Treatment

Rationale for Its Use in a Developing Country

Despite the potential for reasonable shunt outcomes in SSA, the obstacles to treatment access discussed above eliminate the safety net for shunt maintenance that we rely on in more developed nations. Once the fontanels of a child with a shunt are closed, an emergency shunt malfunction in a rural, “up country” location may end in disaster. For this reason, at CCHU, we aggressively pursued ETV as the primary treatment.³ We noted a lower risk for infection for ETV (<1%) compared with our shunt infection risk of around 10%. Also, most ETV failures occur within the first 6 months of treatment, when the fontanel is open and treatment failure tends to be visually obvious and less precipitous—in contradistinction to shunt failures, which continue to occur over the lifetime of the patient and can lead to rapid clinical deterioration.

Combined Endoscopic Third Ventriculostomy and Choroid Plexus Cauterization

The initial experience with ETV was encouraging, but we found, as have others, that young age increases the risk for ETV failure.³ Acting on the hypothesis that this was the result of decreased CSF absorption among infants with congenital causes of HC (e.g., aqueduct stenosis, fourth ventricular outlet obstruction), we began including lateral ventricle CPC bilaterally along with ETV to treat the residual “communicating” HC¹² (► Fig. 5.3). We found that for infants younger than 1 year of

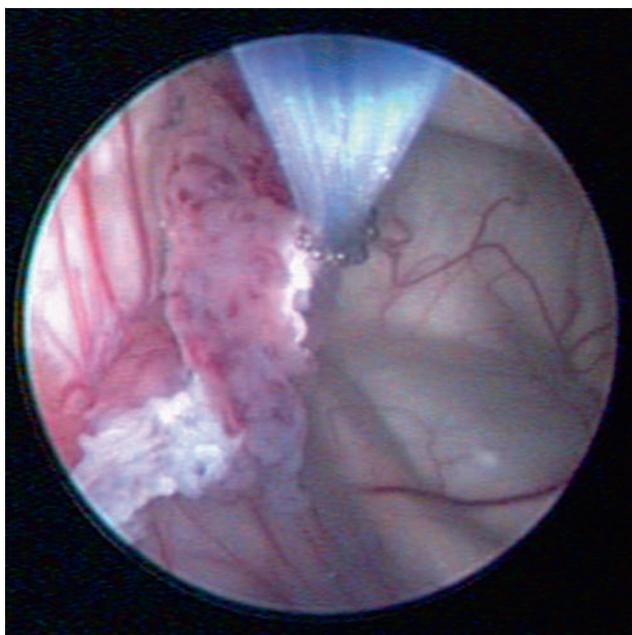


Fig. 5.3 Cauterization of choroid plexus in the lateral ventricle. Monopolar electrocauterization was performed with a Bugbee wire.

age, the addition of CPC significantly increased the overall success of ETV from 47% to 66% ($p < 0.0001$). The operative technique employed for the combined ETV/CPC procedure has been previously described in detail.^{12,13}

We subsequently demonstrated the efficacy of the combined ETV/CPC procedure for subsets of infants with HC of distinct etiologies, including postinfectious hydrocephalus (63.3%), myelomeningocele (76% success), encephalocele (79% success), Dandy-Walker complex (74%), and congenital aqueduct stenosis (81.9%).¹²⁻¹⁷ It is notable that the median age at the time of ETV/CPC in these reports was 2.0 months for infants with myelomeningocele, 3.0 months for infants with postinfectious HC, and 3.1 months for those with congenital aqueduct stenosis. Thus, these results are relevant for infants younger than 3 months of age. For infants with postinfectious HC, the outcome for ETV was more affected by the status of the aqueduct (open or closed) and the prepontine cistern (scarred or open) than by whether CPC was performed.^{12,14} Cisternal scarring is an especially good predictor of failure in these patients, more than doubling the risk for failure after control for other factors.¹⁸ Based upon our first attempt at ETV in 1400 patients, we were able to construct a success prediction score based upon patient age, the etiology of HC, and the extent of CPC.¹⁹ We are working to refine this by using the additional parameters of aqueduct and cistern status.

Mode of Hydrocephalus Treatment and Developmental Outcome

We were concerned that despite the potential benefits of being shunt-independent, there might be some developmental advantage to the treatment of HC by shunt placement, given the general impression that the ventricles tend to remain larger after ETV than with shunt placement. However, in a spina bifida

cohort, we were unable to detect any difference in early childhood development between children treated endoscopically and those treated with shunts.²⁰ Thus, there was no apparent developmental advantage for HC treatment with shunts that would dissuade us from continuing to pursue ETV/CPC as our primary treatment option.

Mode of Hydrocephalus Treatment and Survival

Our original impetus for pursuing endoscopic treatment was the assumption that shunt dependence would increase mortality in the long run, and thus its avoidance would actually save lives. However, we demonstrated no significant difference in 5-year survival between children treated by shunt placement and those successfully treated by ETV or ETV/CPC for myelomeningocele or postinfectious HC.²¹ The majority of deaths occurred from non-HC-related causes (mostly infectious diseases and malnutrition), and they were sufficiently common to obscure any small difference in survival that might have existed between the treatment groups. It was concerning that for these two groups of children, all of whom had some degree of disability, either from the myelomeningocele/Chiari type 2 malformation or the initial brain injury resulting from the neonatal infection causing postinfectious HC (which results in varying degrees of cerebral palsy), the 5-year survival was significantly less than that for their unaffected peers in Uganda. The 5-year survival of Ugandan infants in the general population is reported to be 84% (a child mortality rate of 16%). In the survival studies we conducted at CCHU, we found the 5-year survival for infants treated for postinfectious HC, myelomeningocele, and encephalocele to be 70.5%, 63%, and 61%, respectively.^{13,15,16} The increased mortality may have been related to several factors, including reduced access of disabled children to routine medical care, unrecognized symptoms of HC, or lack of care by their families. We found that the only factor favoring 5-year survival for the children with spina bifida was referral to a community-based rehabilitation program that included regular home visits. These children had significantly better 5-year survival (80%), which was equivalent to that of their unaffected peers.¹⁶ Patients who were not enrolled in one of these programs were three times more likely to die.

Effect of Prior Endoscopic Treatment on Subsequent Shunt Survival

We were concerned that for those patients in whom ETV was abandoned for shunt placement or for those undergoing shunt placement in the face of a successfully completed, but failed, ETV (\pm CPC), there might be an increased risk for shunt infection or obstruction as a result of the endoscopic procedure. However, in a retrospective study of 900 consecutive shunt placements at CCHU, we found no difference in risk for shunt infection or failure among patients who received a shunt primarily, at the time of an abandoned ETV (\pm CPC), or following a completed but failed ETV (\pm CPC).²²

Economic Impact of Primary Endoscopic Treatment

In the CCHU experience, in which 60% of patients have postinfectious HC, the ETV attempt has to be aborted in about 30% of

patients because of anatomical distortion (primarily from prior ventriculitis in those with postinfectious HC). Nonetheless, about half of all patients presenting for treatment are successfully treated with a single endoscopic operation and avoid shunt dependence. The average total financial cost of endoscopic treatment at CCHU in 2005 was \$670, and the cost of initial shunt placement was \$470 (when the inexpensive Chhabra shunts were used, each of which costs less than \$40).²² However, with a conservative estimate of two anticipated shunt revisions over time, and ignoring the additional cost for shunt infection, the total cost of initial placement and subsequent maintenance of shunt function was determined to be \$1,545 over time.²² Avoiding this cost in 50% of patients by attempting endoscopic treatment in all patients would create a potential savings of \$43,750 for every 100 patients presenting for treatment, an appreciable amount in resource-poor settings.

Training

Given the apparent advantages of attempting endoscopic treatment for HC as the primary method, we have advocated the training and equipping of neurosurgeons in developing countries in these techniques. The level of sophistication and skill required by the variable and sometimes difficult anatomy and the medical fragility of many of these infants have compelled us to focus our training efforts on neurosurgeons, although we have successfully trained nonneurosurgeons from regions with no neurosurgeons in certain very select cases. Through CURE Hydrocephalus, a division of the Christian nongovernment organization CURE International, fellows in neurosurgery are trained at CCHU, and after successful completion of their training, their home institutions are provided with the necessary equipment to develop their own programs. CURE Hydrocephalus also hires a local HC clinical coordinator for patient follow-up, given our reported observation that a home visit program may independently reduce mortality.¹⁶

Conclusion

It is unrealistic to expect long-term successful treatment of infant HC in developing countries with the model of visiting surgical teams that place shunts but are unable to provide follow-up or future access for the maintenance of shunt function. An argument can be made for placing the highest priority on training and equipping centers to provide competent longitudinal care. Furthermore, a strong case can be made for a policy of endoscopic treatment as the primary intervention, either by intention to treat in all patients or by refining the selection criteria according to established predictors of ETV success. The primary treatment of infant HC by ETV/CPC is more likely to be effective than ETV alone, and this treatment paradigm can dramatically reduce the incidence of shunt dependence—an especially important outcome in the context of countries with limited resources. This approach does not appear detrimental to developmental outcome, nor does it increase the subsequent risk for shunt malfunction or infection for those children in whom a shunt is ultimately required. The majority of ETV/CPC failures occur within the first few months of surgery, during a relatively safe period of infancy when failure is visibly obvious to the family and is not an acute emergency. Furthermore, a

paradigm of intention to treat by endoscopy may be more cost-effective in a given population. The increased mortality we have observed in disabled children can be mitigated with community-based rehabilitation or home visit programs, which should ideally be a component of any regional HC treatment center in the setting of a developing country.

5.1.2 Meningoceles and Myelomeningoceles

The incidence of meningocele (MC) and myelomeningocele (MMC) in developing countries appears to be significantly greater than that in developed countries, partly because of the lack of folic acid in diets, partly because of the ingestion of maize contaminated with the mycotoxin fumonisin (a folate antagonist),²³ partly because of the lack of prenatal screening and abortion, and partly because of the high birth rates in developing countries, such that the number of any congenital abnormalities would be increased. Approximately 300 infants come to Kijabe Hospital each year with untreated MMC. Few mothers of infants with MMC have heard about the benefit of folic acid in reducing the risk for MMC; they are given a year's supply of folic acid when their baby is discharged.

MC in developing countries seems to occur in the same ratio to MMC (~1:20) as in developed countries and to have the same presentation, imaging characteristics, treatment, and outcomes as in developed countries. However, MMC has a different spectrum; infants seem to have higher lesions, to have a greater likelihood of paraplegia or of an associated kyphus or split-cord malformation, and to be born with substantial HC.

Developing countries have few, and sometimes no, facilities to care for infants with MMC. Neurosurgeons and multidisciplinary care are rare, and if care is provided, it is often by a general surgeon who closes the back and/or inserts a VP shunt. Because children with MMC are a substantial drain on family resources, they are often not taken for treatment, and many die within a few months. Some centers insert a shunt but do not close the MMC, thinking that the baby's death would be the best outcome for both it and the family, and that in those infants who do survive, epithelium and then scar tissue will develop over the MMC.

MMC is rarely detected prenatally. Many deliveries occur at home or in rural hospitals, and transfer to facilities where care is available may be delayed because the family has insufficient funds to pay for the transportation, much less the medical care. Thus, although most children with MMC present within 2 months after birth, some do not present until 2 to 3 years later. When infants present within a few days after birth, some MMCs have ruptured. Even those that are intact may have become infected. In Kijabe, we analyze CSF from both the MMC sac and the ventricles on admission. CT or MR imaging is rarely available (or needed) before closure of the MMC, but lateral spine X-rays are helpful in evaluating kyphotic deformities (► Fig. 5.4).

The ethical aspects of closing MMCs in developing countries are complex and beyond the scope of this chapter. In Kijabe, we offer operations to nearly all children with MMC, but there are a few for whom the prognosis is so dismal that palliative care seems appropriate—for example, infants with MMC, severe malnutrition, and gram-negative ventriculitis.

At operation, some surgeons close the MMCs as they are closed in the United States, in-folding the lateral edges of the

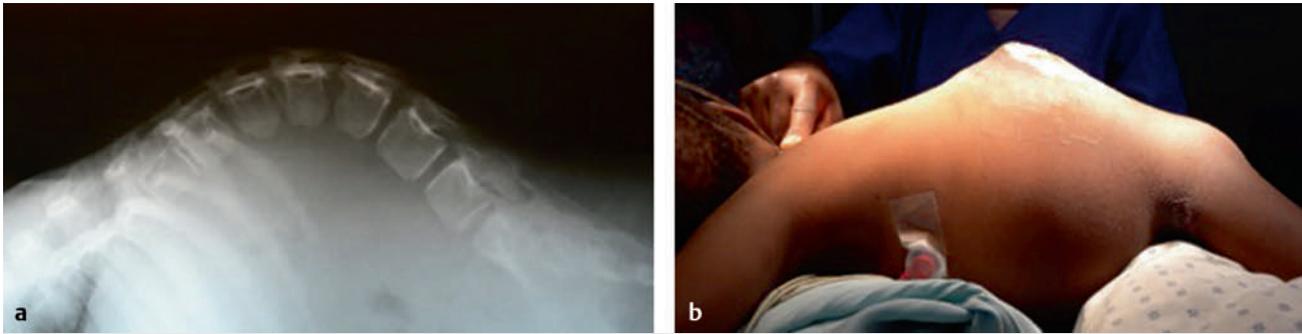


Fig. 5.4 Lateral spine radiographs of (a) an infant with a congenital kyphotic deformity associated with a myelomeningocele and (b) a 2-year-old child with a myelomeningocele-kyphotic deformity that was unrepaired at birth.

placode to the midline to “reconstitute” the cord, then covering it with semicircular leaflets of dura, then subcutaneous tissue and skin. However, a case can be made for doing distal cordectomies at the junction between the spinal cord and neural placode. Because placodes have minimal if any function, in our experience with many cases, motor function is rarely lost after distal cordectomies, and the risk for a subsequent tethered cord is probably decreased. For children who present with both MMC and clinically significant HC, a combined MMC closure and VP shunt or ETV/CPC can be considered *if* the child is afebrile, has a normal complete blood count, and has fewer than five white blood cells in CSF from the ventricles and from the MMC sac. In our Kenyan experience, approximately 15% of infants have an associated kyphus underlying the MMC. Because untreated kyphus frequently progresses in the following years, removal of the kyphotic vertebra and realignment of the spine by kyphectomy can be considered,²⁴ and this is performed routinely in Kijabe. Adjacent vertebral bodies can be held in alignment with large sutures (e.g., 0-Prolene) because infant vertebrae are too soft to hold screws, and then stabilized for 3 months postoperatively with a lumbar brace.

The frequency of complications after MMC closure is substantially higher than in the United States. Complications—including wound breakdown, infection, and CSF leak—occur in perhaps one-third of cases and reflect the underlying malnutrition, poor wound hygiene, and thin, taut tissues. Within the first week after operation, infants are begun on clean, intermittent bladder catheterization (CIC). Three months postoperatively, urodynamic studies and renal ultrasound scans are done to evaluate the need for continued CIC.

Follow-up care is usually infrequent and decreases as the children get older. Mortality data from Uganda with a 98% cohort follow-up indicate a 63% 5-year survival, with a threefold difference in survival between those who are in community follow-up programs and those who are not. Survival also depends on factors such as regularity of clean intermittent catheterization, development of decubiti, and availability of medical resources to evaluate and treat complications.

5.1.3 Lipomyelomeningoceles

Children with lipomyelomeningocele (LMMC) present from infancy throughout childhood, sometimes because of the obvious subcutaneous lumbar mass and sometimes because of pain,

bladder dysfunction, or leg weakness associated with the mass and tethered cord. Preoperative MR images are usually not available. Operations for children with LMMC should be done only by neurosurgeons experienced with these lesions; they are far more complex than those for MMC, and the frequency of complications is far higher. It is not uncommon to see a child in whom the superficial component of an LMMC had been excised by a general or pediatric surgeon who did not realize the underlying intraspinal component and tethered spinal cord. For neurosurgeons experienced in the care of children with LMMC, the surgical indications are the same as they are in developed countries. If an experienced neurosurgeon is not available, a case can be made to wait until neurologic signs or symptoms develop, a treatment paradigm supported by those who advocate that practice routinely.

Intraoperatively, the periphery of the fatty subcutaneous mass is exposed, then normal spinal cord cephalad to the LMMC is exposed through a laminectomy. Under magnification, the LMMC is dissected off the spinal cord; lasers are not available, but a needle tip cautery set at low voltage works acceptably. In general, the older the child, the more difficult the operation. The goal of operation is to untether the spinal cord, not to completely resect the mass and all intradural fat. The dura should be closed meticulously and the closure supplemented with overlying muscle and fascia if possible to decrease the risk for postoperative CSF leaks. In the Kenya experience, postoperative CSF leaks develop in perhaps half of the children, and closure of the leaks may require multiple procedures, occasionally even the insertion of a VP shunt. Morbidity of the operations depends on the anatomy of the lesion and the expertise of the neurosurgeon. The likelihood of recurrent LMMC tethering in developing countries is unknown, but it is probably similar to that in developed countries if children undergo similar operations.

5.1.4 Split-Cord Malformations

Split-cord malformation (SCM) appears to be more common in developing countries. In the Kenya series of patients with MMC operated on in infancy, approximately 15% have an associated SCM. An infant born with an MMC and asymmetric neurologic function in the lower extremities is more likely to have an SCM than a hemimyelomeningocele. The classic SCM indicators of lumbar hypertrichosis and scoliosis are uncommon in infants but

are often present in older children. Many SCMs are found only at the time of operation because many children undergo surgery on the basis of clinical signs and symptoms, without antecedent CT and MR imaging. The SCM may be associated with lipomeningoceles, neurenteric cysts, or other congenital anomalies.

The intraoperative treatment of SCM is similar to that in developed countries. In the series of 300 cases of SCM reported by Mahapatra, 20% of the patients with a neural tube defect had an SCM.²⁵ In his patients with SCM, skin stigmata were present in 65%, scoliosis in 50%, and foot deformities in 48%; motor and sensory deficits were present in 80% and 70%, respectively; postoperatively, 50% improved, 44% stabilized, and 6% worsened. Prophylactic operations are probably advisable for asymptomatic patients if experienced neurosurgeons are available because of the risk for insidiously worsening neurologic function and the difficulty of good follow-up over the years.

5.1.5 Chiari Malformations

Chiari type 1 malformations are rarely diagnosed in developing countries, primarily because MR imaging is rarely available to evaluate children who present with either posterior pain at the craniovertebral junction or scoliosis secondary to a syrinx. In infants with MMC, Chiari type 2 malformations may cause cervical hyperextension, swallowing difficulty, nasal regurgitation, aspiration, and stridor in the first 2 to 3 months after birth. In symptomatic infants, if the associated HC has not been treated, it should be. If infants are symptomatic and have a functioning shunt or ETV, Chiari decompressions can be considered if surgeons experienced with such operations are available. The operations can be done without preoperative imaging; the surgeon performs cervical laminectomies and dural opening from the foramen magnum caudally until the bottom of the herniated vermis is identified. A dural graft of pericranium or cervical fascia suffices if no cellulose grafts are available. Infants with Chiari type 2 malformations that are symptomatic at birth have such a poor prognosis that decompression is probably not advisable.

5.1.6 Encephaloceles

The ratio of occipital encephaloceles to frontal encephaloceles is approximately 50:50 in many developing countries, although in the Ugandan experience 48% were occipital, 30% sincipital, and 22% parietal.²⁶ Most children with occipital encephaloceles present within the first 6 months of life; the median age in Uganda was 1 month, with a mean of 17 months, and the mean age in Kenya was 4 months.²⁷ Encephaloceles are usually covered by skin, although occasionally by a membrane that may have ruptured. Surgical treatment involves resection of the abnormal skin and dural sac—leaving enough dura and skin to close the defect without undue tension—and involves the resection of herniated brain tissue. Although “expansion cranioplasties” have been reported as a means of preserving herniated brain, there is no evidence that neurologic function is improved if cerebral tissue in the encephalocele is preserved.²⁸ Alternatively, a frontal cranial expansion can be done to increase intracranial volume and allow the herniated contents to be positioned intracranially (A. K. Mahapatra, personal communication, 2012). Clinically significant HC developed in 33% of

children in the Ugandan series and in 36% in the Kenyan series.^{26,27} HC may be treated by ETV, ETV/CPC, or VP shunt. In the Ugandan series, 35 required treatment of HC—13 with ETV/CPC, 2 with ETV alone, and 13 with VP shunt. Successful treatment at 1 year was greater after ETV/CPC (79%) than after VP shunt (47%).

Children with sincipital encephaloceles seem to present at any age, from infancy onward. In an Indian series of 133 cases, 15 patients were 5 to 18 years old and 10 were older than 18 years.²⁹ In most large series, frontoethmoidal encephaloceles predominate. Cerebral tissue is present in sincipital encephaloceles, but the amount of tissue within them is generally less than in occipital encephaloceles, and the children are more likely to be mentally normal or nearly normal. HC has been reported in 17 to 36% of sincipital encephaloceles and agenesis of the corpus callosum in 12%.^{26,30} In our experience, most frontal encephaloceles are usually repaired best by combined facial and intracranial approaches, although in the Cambodian series, 21% of cases were treated by a transcranial approach, without a facial incision.³¹ Hypertelorism frequently accompanies frontal encephaloceles and may be treated by the classic Tessier procedure or by medial repositioning of the medial orbital walls.^{30,32}

5.1.7 Craniosynostosis

In the United States, sagittal and metopic synostoses predominate; in developing countries, coronal and syndromic synostoses are more common.³³ Cranial deformities associated with craniosynostosis (CS) in developing countries are often considered to be cosmetic problems not requiring medical intervention, and children are often brought for medical evaluation long after infancy (► Fig. 5.5). CS in developing countries is treated only in centers with neurosurgeons and is therefore uncommon. Even in centers where a neurosurgeon is present, operations are infrequent: Balasubramaniam and Rao reported only 70 cases in 10 years.³³ Orbitofrontal advancements in developing countries rely on stainless steel wires for bone fixation because absorbable or titanium plates and screws are rarely available.

5.2 Tumors

5.2.1 Scalp and Skull Masses

The most common location for a subcutaneous dermoid cyst in the United States is at the lateral aspect of the eyebrow. In Kenya, the most common location is at the anterior fontanel, where the cyst enlarges slowly but inexorably until removed, sometimes reaching a diameter of 8 to 10 cm in teenagers. Although dermoid cysts in infants erode the underlying bone, giant dermoid cysts seem to do so less often.

Eosinophilic granulomas have been seen less often in our experience than in the United States, but when they occur, they present in the same way—as tender, subcutaneous masses that develop after infancy, with irregular, moth-eaten, lytic skull defects visible on X-ray films. Although some eosinophilic granulomas regress over time when evaluated by repeated examinations and X-rays, such watchful waiting is less appropriate in developing countries because follow-up visits are more difficult for the families and therefore less likely to occur.



Fig. 5.5 Untreated Kleeblattschadel deformity in a 7-year-old child who presented for medical evaluation of an unrepaired abdominal omphalocele.

5.2.2 Supratentorial and Infratentorial Tumors

Children with brain tumors present late, and they are often blind because of chronic untreated HC and often cachectic because of repeated vomiting and poor nutritional intake. The tumors are more likely to be diagnosed by CT scans than by MR images, and they are usually large.

The surgical goal of treating children with supratentorial gliomas is similar to that in developed countries—total or extensive resections, which, because of the dearth of instruments like ultrasonic aspirators, are frequently done with suction, bipolar cautery, and pituitary forceps. The scarcity of postoperative radiotherapy and chemotherapy increases the importance of maximal resections. The management of craniopharyngiomas is particularly problematic. If tumors are predominantly monocystic, the intracystic injection of bleomycin (2 to 3 mg three times a week for 3 to 5 weeks) via a subcutaneous reservoir and intracyst catheter is appropriate.³⁴ When a craniopharyngioma is associated multiple large cysts above the inferior solid tumor component, the cysts can be effectively removed via a transcallosal approach to “buy time” for the child to reach an age when radiotherapy has fewer complications. It is appropriate to

attempt complete resection of a craniopharyngioma only in the rare circumstances in which the family has the means of providing lifelong multiple-hormone replacement and the neurosurgeon has considerable experience with such resections.

The same four infratentorial tumors—pilocytic astrocytomas, medulloblastomas, ependymomas, and brainstem gliomas—occur in developing countries as in developed ones, but their management differs considerably because of the infrequent availability of postoperative radiotherapy and chemotherapy. The only posterior fossa tumors treated similarly in developing countries are pilocytic astrocytomas, for which the operative goal is complete excision. Ependymomas—whose prognosis is so greatly improved by complete resections—are less likely to be completely resected if they invade the brainstem; if the resection results in the need for a gastrostomy or tracheostomy, those modalities are associated with enormous problems after the child is discharged. Medulloblastomas are often subtotaly resected if a frozen section confirms the diagnosis, and postoperative staging with CSF analysis and craniospinal imaging with MR is rarely available or done. If postoperative craniospinal irradiation is done, it is often administered empirically with standard doses of radiation, without postoperative imaging of the spinal axis. If a diffuse brainstem glioma is demonstrated on scans, children are treated palliatively with corticosteroids and analgesics; there is no indication for operation, and their prognosis is too poor to use the limited radiotherapy resources.

5.3 Trauma

Most pediatric head injuries are managed by nonneurosurgeons. Closed head injuries are managed with intravenous fluids and (inappropriate) dexamethasone, without intracranial pressure monitoring or scans. If no scanner is available, the surgeon can make a bur hole at the coronal suture in the midpupillary line, insert a needle into the lateral ventricle, and inject air for a ventriculogram. If the ventriculogram demonstrates a midline shift of 1 cm or more, bur holes in the temporal region are indicated to determine if a hematoma is present, a traditional technique we have used on several occasions. Alternatively, the traditional technique of making three bur holes, one in the temporal region, one in the posterior frontal region, and one in the parietal region, will detect many hematomas. Open head injuries are often treated by general surgeons by closure of the scalp, with or without irrigation and débridement. The morbidity and mortality of traumatic brain injuries are far higher in developing countries than in developed countries.

5.4 Infectious Disorders

5.4.1 Brain Abscesses

Brain abscesses are relatively common in developing countries. Contributing factors include a higher incidence of immunosuppression associated with AIDS and incompletely treated otitis media. Otitis media has been the most common source of brain abscesses in developing countries, followed by scalp and skull abscesses and by cyanotic heart disease.³⁵ Abscesses are solitary in about 80% of cases, but the prognosis of children with multiloculate abscesses appears to be similar to that of children with

a solitary abscess. Pus from brain abscesses was cultured in a series of 118 Indian patients, and microorganisms were identified in 81 to 75% by culture and in 6% by Gram stain; 64% of the organisms were aerobic and 31% anaerobic, and 5% were mycobacteria and 1% fungi.³⁶ The most common organisms were *Streptococcus viridans* (24%), *Staphylococcus aureus* (14%), *Bacteroides* (10.5%), and *Peptostreptococcus* (10.5%). The overall mortality was 14.4%, with more deaths in patients with gram-negative infections (30%) than in those with gram-positive infections (9.5%).

Neurosurgical treatment is limited to children with abscesses of appreciable size (≥ 3 cm) and in locations that can be aspirated via a bur hole. Excision of an abscess capsule is rarely indicated. Two effective techniques are to localize the abscess with ultrasound guidance and to aspirate as much pus as possible, then to treat with antibiotics. Repeated aspirations are sometimes needed. Alternatively, a bur hole can be made and a red rubber catheter inserted into the center of the abscess to aspirate pus (which should be taken immediately for culture), leaving the catheter in the cavity and inserting a sterile safety pin through the catheter at the level of the scalp to prevent its inward migration. The catheter is transected 1 cm distal to the safety pin and gauze applied over the open distal end of the catheter to collect purulent drainage. The catheter can be shortened by 5 to 10 mm per day until it is out. Postoperative antibiotics usually consist of third-generation cephalosporins and metronidazole, often supplemented with intravenous chloramphenicol, which is rarely used in developed countries but has broad coverage of gram-positive and gram-negative organisms and good CSF penetration.

5.4.2 Tuberculomas

Tuberculomas are covered comprehensively in Chapter 79.

5.5 Spasticity and Movement Disorders

Children in developing countries with focal spasticity of the upper extremities can be effectively treated by selective fasciculotomies. Puligopu and Purohit treated 20 patients, mean age 13 years, with selective motor fasciculotomies of the musculocutaneous nerves (13), median nerves (24), and ulnar nerves (3) and observed significant reduction in spasticity and improvement in hand function.³⁷ Lumbar dorsal rhizotomies are effective treatment of spastic diplegia and can be done in resource-poor environments. Lumbar dorsal rhizotomies can be done effectively without neurophysiologic monitoring, with proportions of the dorsal nerves (usually 50 to 75%) divided based on the severity of spasticity in the affected muscles.³⁸ Monitoring responses is inconsistent, and in the experience of both authors, outcomes are no different whether monitoring is or is not used.³⁹ For children with spastic quadriplegia who require tone reduction in the upper and lower extremities to facilitate care or to diminish the development of contractures, combined cervical and lumbar dorsal rhizotomies performed during the same anesthetic session can provide effective relief. Children with focal dystonia of an upper extremity can be treated by cervical dorsal ventral

rhizotomies, dividing about 85% of the ventral roots to the upper extremities.⁴⁰

In developing countries, intrathecal baclofen and deep brain stimulation are essentially unavailable. We know of no good neurosurgical treatment for children with generalized dystonia or choreoathetosis that has not responded to oral medications.

Pearls

- Socioeconomic factors beyond the control of the neurosurgeon—such as malnutrition, anemia, poor hygiene, and concurrent illnesses—play a major role in the condition at presentation and the outcomes of children with neurosurgical disorders in developing countries.
- HC secondary to neonatal ventriculitis is far more common in limited-resource countries than in developed countries. The prevention of severe macrocephaly (head circumference > 60 cm), whether by VP shunt or ETV/CPC, markedly eases caregiver burden.
- The efficacy of the combined ETV/CPC procedure for infants with postinfectious HC is approximately 65%; for MMC, 75%; for encephalocele, 80%; for Dandy-Walker complex, 75%; and for congenital aqueduct stenosis, 80%.
- The 5-year survival rates of infants treated for postinfectious HC, MMC, and encephalocele are approximately 70%, 63%, and 61%, respectively.
- Infants with MMC, minimal lower extremity function, and associated kyphus can be effectively treated by distal cordectomy and kyphectomy when the initial MMC closure is done; distal cordectomy seems to be associated with no significant increase in neurologic deficit and may be associated with a lower risk for subsequent tethered spinal cord.
- Children with LMMC have a substantially higher rate of postoperative complications—particularly CSF leaks—than those with MMC and should be operated on only by neurosurgeons experienced with these procedures.
- Children with focal spasticity, spastic diplegia, or spastic quadriplegia can be effectively treated by peripheral fasciculotomies or dorsal rhizotomies, without electrophysiologic monitoring.

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6 Ethical Issues in Pediatric Neurosurgery

Patrick J. McDonald and Nalin Gupta

Although there is no one definition of the term *ethics*, in general it encompasses the various approaches to understanding and examining moral behavior.¹ The study of ethics can be broadly classified into two areas: normative ethics and nonnormative ethics. Normative ethics seeks to answer the question “What ought I to do?” for a given moral dilemma, whereas nonnormative ethics simply describes how people reason and act in moral situations, without commenting on the inherent “rightness” of their actions. From Aristotle to Aquinas to Kant to Rawls, philosophers have for millennia written about morality and what constitutes ethical behavior.

The application of ethical principles to health care decision making, however, is a relatively young field. Various descriptions as *bioethics*, *biomedical ethics*, and *medical humanities*, among others, as a branch of normative ethics it seeks to define, analyze, and guide decision making in medicine as it relates to the moral issues that confront both health care providers, patients, and their families or surrogates. The formal, if somewhat cumbersome, definition of bioethics is “...the systematic study of the moral dimensions—including moral visions, decisions, conduct, and policies—of the life sciences and health care, employing a variety of ethical methodologies in an interdisciplinary setting.”²

The last three decades have seen tremendous growth in the field of biomedical ethics. Virtually all medical schools and many residency programs incorporate ethics teaching and/or training into their curricula.^{3–6} While the issue of whether one can teach “virtuous behavior” to a physician (or any other individual, for that matter) remains contentious, there is little doubt that the proliferation of ethics teaching has resulted in a heightened awareness of ethical issues and dilemmas in medicine.

There is perhaps no other specialty in medicine that is confronted with ethical issues and dilemmas on a daily basis more than pediatric neurologic surgery. On an ongoing basis, pediatric neurosurgeons make medical decisions regarding problems ranging from severe congenital nervous system malformations, to premature newborns, to quality-of-life and end-of-life issues that have profound ethical, spiritual, and religious consequences.

The purpose of this chapter is to trace the history and development of modern biomedical ethics, review the basic principles of ethics and ethical frameworks, and provide an overview of some of the more common ethical issues faced by pediatric neurosurgeons. In addition, specific issues commonly encountered in practice are analyzed in an attempt to provide pediatric neurosurgeons with the tools necessary to assist them in reaching decisions when confronted with difficult ethical situations.

A common misconception regarding bioethics and those who provide an ethics consultation service is that there is one “right” answer for a given moral or ethical dilemma. Those who have sought the opinion of ethicists may often complain that in the end they are not given enough direction as to the correct course of action; in essence, they are not given an “answer.” Often, the correct course of action is profoundly influenced by the experience, cultural background, priorities, and subjective desires of the individuals involved, as well as their perceptions

of the importance of the issues at hand. Similarly, this chapter does not purport to have any one answer for all the ethical problems encountered in the practice of pediatric neurosurgery. We cannot be worse off, however, for having examined in a critical and thoughtful way, from our own personal standpoint, the difficult issues that confront our young patients and their families. In the end, this ongoing reflection may, and perhaps should, result in a continual re-evaluation of our own biases toward what “one ought to do.” A bioethical analysis resides in a middle ground between things that seem to be incontrovertibly factual and those that are entirely subjective.

6.1 History of Biomedical Ethics

The roots of bioethics date back to the fifth century BC, when Hippocrates, considered the greatest physician of his era, codified his understanding of how a physician should act into the Oath of Hippocrates. Medical students today still recite a modified version of the original oath upon graduation. The birth of modern-day bioethics occurred in the late 1940s, largely in response to the atrocities committed by Nazi physicians during the Second World War. The trial of Nazi doctors at Nuremberg, Germany, from 1946 to 1947 resulted in the formulation of the Nuremberg Code, which outlines a list of requirements for the ethical conduct of research on human subjects.⁷ The Nuremberg Code has been largely replaced by the World Medical Federation Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects, last revised in 2008.⁸

What is now recognized as the field of bioethics began to evolve in the 1960s in response to rapid changes in medical technology and therapies. Over the course of the last three or four decades, bioethics has staked a claim as a distinct discipline within the traditional health sciences. Many health care institutions now have clearly identified ethics departments, usually functioning as a consultative service to other clinical departments, in addition to existing hospital ethics committees and institutional review boards (IRBs) or research ethics boards (REBs). Clinical bioethicists come from varying backgrounds, including philosophy, medicine, nursing, and law. Although the field is relatively new, the questions it seeks to address are timeless: “They turn on the meaning of life and death, the bearing of pain and suffering, the right and power to control one’s life, and our common duties to each other.”²

6.2 Ethical Frameworks

In both the teaching of bioethics and the application of bioethics to clinical medicine, ethicists use a variety of ethical frameworks—specific lenses through which a particular ethical issue can be seen—to better outline the crux of the ethical matter at hand. Although not an exhaustive summary, the following paragraphs give a brief introduction to some of the more commonly used ethical frameworks. For those interested in further reading about the individual frameworks, more detailed information is available in the references cited.

6.2.1 Principlism

The term *principlism* refers to what are commonly known as the “four pillars” of modern bioethics as outlined by Beauchamp and Childress¹: autonomy, nonmaleficence, beneficence, and justice. These principles are the most commonly taught concepts in bioethics in medical schools today and are summarized below.

Respect for Autonomy

Autonomy (derived from the Greek words for “self-rule”), simply put, respects the ability of competent persons to make informed decisions regarding their medical care. In the last 30 years, the concept of autonomy has superseded the tradition of beneficent paternalism, in which patients essentially trusted that their physicians would make appropriate decisions, both medically and ethically, on their behalf. Autonomy is at the core of the concept of informed consent, in that a person cannot make a truly autonomous decision without fully understanding the risks, benefits, and alternatives to the proposed therapy. Pediatric neurosurgeons deal with the difficulties associated with the concept of autonomy in that many of our patients, by virtue of their age, disease, and developmental status or because of statutory restrictions, do not have the ability to make decisions on their own. As such, we must rely on substitute decision makers—in most cases, their parents. A common criticism of Western bioethics is the perceived overemphasis on the principle of autonomy.

Nonmaleficence

Primum non nocere (“first do no harm”), based on Hippocratic principles, effectively summarizes the principle of nonmaleficence. Because virtually every intervention in medicine, especially in pediatric neurosurgery, carries with it the potential to do harm, it may be better to express the principle of nonmaleficence in terms of exposure to undue risk of harm or deliberate intent to harm. The principle of nonmaleficence and the importance of intent are often cited when withholding versus withdrawing treatment and killing versus letting die are contrasted.

Beneficence

Beneficence refers to the act of doing or producing good or performing acts of kindness and charity.⁹ In the context of medical interventions, the intent or hoped-for outcome of an intervention must have a reasonable chance of producing some benefit to the patient or, conversely, of preventing or lessening the harm coming to the patient from his or her disease.

Justice

Perhaps the most controversial of the four principles, justice is variously described as what is fair or deserved, or what one is entitled to. “Distributive” justice “...refers to fair, equitable, and appropriate distribution determined by justified norms that structure the terms of social cooperation.”¹ The allocation of health care resources at all levels (micro, meso, and macro), rationing, and priority setting in health care institutions are all issues in which the principle of justice plays a key role.

Although beyond the scope of this chapter, the ongoing heated debate on health care reform in the United States centers on different interpretations of the definition of justice as it applies to the allocation of health care resources.

6.2.2 Utilitarianism and Consequentialism

Based on the theories of the 19th century philosophers Jeremy Bentham and John Stuart Mill, utilitarianism states that the moral worth of an action is determined by its consequences.¹⁰ Moral decisions should seek to maximize the good; that is, given choices, one should choose that action that results in the greatest good for the greatest number of people. This is known as the principle of utility.

Utilitarian arguments are often used when decisions are made regarding the allocation of scarce resources in health care, such as the funding of expensive new technologies and the distribution of donated organs for transplant. One of the major criticisms of utilitarianism is that in theory it allows the interests of the majority to override what may be legitimate claims or rights of the minority. A utilitarian might argue that in pediatric neurosurgery, a resource-intensive subspecialty, funds could be more effectively utilized by diverting them to better prenatal care. Utilitarianism is a form of consequentialism, an ethical theory holding that the morality of an act is determined entirely by the consequences of that act.

6.2.3 Duty-Based Frameworks and Kantianism

In direct contradiction to consequentialist or utilitarian theory is the duty-based or “deontological” theory of moral reasoning. The work of the 18th century Prussian philosopher Immanuel Kant, *Critique of Pure Reason*, is the basis of duty-based ethical frameworks, and this moral framework is more popularly known as Kantianism. Kant’s “categorical imperative” states that one “...should act only according to that maxim which you can at the same time will that it become a universal law.”¹¹ Thus, the moral worth of an action is based on whether it conforms to this rule of obligation. These obligations or imperatives can be derived from pure reason and are not dependent, according to Kant, on culture, tradition, or emotion. As an example, for Kant, truth telling is always morally obligatory, as one cannot construe a maxim in which lying would be considered universally acceptable. A major criticism of duty-based or Kantian moral theory is that it offers no solutions when duties or obligations conflict.

6.2.4 Communitarian Ethics

In contrast to the largely rights-based, individualistic theories summarized above, communitarianism seeks to make moral decisions based on communal values, goals, and traditions rather than individual rights and takes issue with more liberal theories that allow individual rights to trump the good of the community. The central question of communitarianism is “What is most conducive to a good society?” rather than “Is it harmful or does it violate autonomy?”¹²

6.2.5 Ethics of Care

Similar to communitarianism, an ethics-of-care framework does not seek to conform to set rules or moral theories. It highlights the role of relationships in making decisions and considers the values encountered in intimate personal relationships, such as love, compassion, fidelity, and sympathy, to be the most important factors in making decisions.^{13,14} Thus, in making a decision about aggressive care for a severely neurologically impaired child, factors such as the relationship of the child with other siblings and the impact of the child's illness on the entire family or community would be considered.

6.2.6 Casuistry

Casuistry is a branch of applied ethics based largely on the reasoning applied in common law. Rather than applying a particular ethical theory or framework to a given problem, casuistry looks at morality by examining cases. The correct course of action is determined by comparing the case at hand to "pure" or "paradigm" cases and determining if a similar course of action as taken in the paradigm case is warranted.^{15,16} For example, for end-of-life issues, the case of Karen Quinlan could serve as the paradigm case.¹⁷ Thus, morality stems from a social consensus as dictated by previous actions, rather than a set of rules or theories.

6.3 Ethical Issues

Some of the more commonly encountered ethical situations in pediatric neurosurgery are presented below, with illustrative cases and an accompanying discussion.

6.3.1 Quality of Life and Futility

The Cases of Baby K and Baby Jane Doe

Baby K was born with anencephaly. At the insistence of her mother, Baby K was intubated and ventilated after delivery. The recommendation for a "do not resuscitate" order was rejected by the mother, and eventually Baby K was weaned from the ventilator. After attempts to transfer the baby to another institution were unsuccessful, she was transferred to a nursing home. Episodes of respiratory distress and apnea resulted in multiple readmissions and an eventual tracheostomy. Despite a court-appointed guardian's recommendation for palliative measures only, the courts ultimately decided that the hospital was obligated to provide emergency treatment for respiratory distress. Baby K eventually died of a cardiac arrest at 2 years of age.

In 1983, Baby Jane Doe was born with an open neural tube defect. After being advised by physicians of a high risk for mental retardation and physical handicap, the parents of Jane Doe decided against surgical repair, despite the surgeon's recommendation that surgery be done, and asked that their child be provided nutrition and comfort measures only.

One of the more controversial topics in bioethics over the past 25 years has been medical futility and, stemming from this, quality of life—specifically, the following questions: Is there a threshold quality of life below which life cannot be considered

worth living, and if so, who makes this decision if the patient is unable to do so? The cases of Baby K and Baby Jane Doe illustrate these concepts.

Futility has been described as comprising four separate types¹⁸: physiologic futility (the intervention will not have its intended physiologic effect); imminent demise futility (the patient will die regardless of the intervention); lethal condition futility (the patient will die, no matter what the treatment); and qualitative futility (treatment is futile because quality of life is so poor). Others define futility as being either quantitative (in the last 100 cases, the proposed treatment has not been successful) or qualitative (the treatment prolongs life but simply preserves unconsciousness and dependence on intensive medical care).¹⁹ Despite these attempts at defining futility, the American Medical Association Council on Ethical and Judicial Affairs summed up the reality of the situation when it stated that "futility cannot be meaningfully defined" and that "denial of treatment should be justified by openly stated ethical principles and acceptable standards of care."²⁰ In the end, no one definition of futility may be adequate for every ethical situation.

In pediatric neurosurgery, decisions regarding futility can often place physicians in conflict with parents or guardians when parents either insist on treatment that a surgeon feels is futile or refuse treatment that the surgeon feels is indicated and in the child's best interests. Appeals to ethical principles do not necessarily resolve the conflict easily, as ethical principles can often conflict, especially with strongly held religious beliefs. A strict appeal to autonomy might dictate respecting the wishes of the parents even if a surgeon feels strongly that continued aggressive treatment or cessation of treatment may violate the principle of nonmaleficence.

When such conflict exists, it is important that neurosurgeons exercise care before deciding on a particular course. We suggest that the following steps be followed, as outlined by Brody and Halevy: (1) Parents or guardians should be involved in the decision-making process early on; (2) second opinions should be sought early and should be seen as a means of helping in the decision-making process; (3) when the conflict seems insurmountable, transfer of care to another physician should be considered; and (4) where available, institutional ethics consultation or review should be utilized.¹⁸ In rare circumstances, when conflicts cannot be resolved, legal remedies through the courts may need to be sought.

Quality of Life and Myelomeningocele—The Groningen Protocol

Euthanasia and physician-assisted suicide have been legal in the Netherlands since 1985. In 2005, pediatricians at the University Medical Center in Groningen, the Netherlands, outlined a protocol for euthanasia in newborns, commonly known as the Groningen Protocol.²¹ This protocol allows the use of lethal injection in newborns, with consideration of the following five criteria: (1) extremely poor quality of life (suffering) in terms of functional disability, pain, discomfort, poor prognosis, and hopelessness; (2) predicted lack of self-sufficiency; (3) predicted inability to communicate; (4) expected hospital dependency; (5) long life expectancy. In addition, parents are required to fully agree, and a team of physicians, at least one of whom is not involved in the care of the patient, must agree. All cases of

infant euthanasia are reviewed by a district attorney, and if the above criteria are not met, a physician may be prosecuted.

During a 7-year period from 1997 to 2004, 22 newborns were felt to meet the above criteria and hence received a lethal injection. Interestingly, all 22 of these infants were felt to have “severe spina bifida.” Not surprisingly, the publication of the Groningen Protocol resulted in considerable controversy and debate. In 2010, Barry published a rebuttal to the assumptions made in the Groningen Protocol, using both ethical and evidence-based principles to argue that “active non-voluntary euthanasia in neonates born with a myelomeningocele (MMC) must be condemned as unethical.”²² Barry argued that available evidence suggests that overall quality of life for persons with MMC is equal to that of age-matched controls.²³ The authors of the protocol argued that euthanasia is justified in infants for whom a life of intolerable suffering is expected. Barry rightly pointed out that there is no evidence that persons living with MMC live with a severe degree of pain and suffering.

The motivation of the authors of the Groningen Protocol was to save affected infants from a life of intolerable suffering and hopelessness—in essence arguing that death is a better outcome than life in these children. Although we agree that there may be circumstances, given extreme amounts of pain, suffering, and cognitive dysfunction, in which death may be a more favorable alternative to the continuation of pain and suffering, with no hope for an acceptable quality of life, it is rare that this is the case in children born with MMC.

The debate surrounding the Groningen Protocol speaks to ethical issues that may never be resolved: What is an acceptable quality of life? Is there a threshold below which life cannot be considered worth living, and if so, who decides?

Quality of Life for the Caregiver

Although one should always act in the best interest of the patient, there are occasions when a surgical intervention may benefit the caregiver more than the child. Neurosurgeons working in developing countries commonly encounter examples of severe hydrocephalus and extreme macrocephaly resulting in significant developmental delay. Surgical treatment in these cases may not alter the long-term neurologic outcome of the child but greatly eases the burdens on caregivers.

6.3.2 Informed Consent and Assent

John is a 16-year-old boy with Ewing sarcoma metastatic to the brain. In addition to the initial treatment of his paraspinal sarcoma, he has undergone a posterior fossa craniotomy to partially resect a dura-based cerebellopontine angle metastasis, followed by radiation and chemotherapy. He presents again with worsening headache and a recurrence of his cerebellopontine angle metastasis, as well as a second metastasis in the right temporal lobe. Repeated surgery followed by stereotactic radiosurgery for residual tumor is recommended as an option, but it is recognized by all that the prognosis is grim.²⁴ His parents wish to proceed with further treatment.

The day before surgery, John asks to speak with you. He states that he knows that it is unlikely he will survive and that he doesn't want any more surgery, but he doesn't want

to disappoint his parents. He says, “If it were up to me, I would refuse to have another operation.”

Parents and guardians have traditionally been considered substitute decision makers for their children when decisions related to health care are made. Many jurisdictions in North America have a statutory age of consent that may correspond to the age of majority in that jurisdiction. The evolution of the process of obtaining informed consent from a patient has paralleled the development of the ethical concept of autonomy; in essence, a competent patient must be fully informed of the risks, benefits, and alternatives to a proposed intervention in order to exercise his or her right to make autonomous decisions. Young patients may not, for the most part, have the capacity to fully understand the consequences of medical decision making and are not considered to be fully autonomous individuals. Given this, we ask their parents or guardians to act as surrogate decision makers.

The basis for surrogate decision making can vary, depending on the particular child and the age of the child. Substitute decision making or substituted judgment, the basis for most surrogate decisions in adults, seeks to determine what individuals would decide for themselves were they able to make the decision on their own. For young children, clearly it is difficult to infer what decision they would make had they the capacity to decide. As such, most surrogate decision making for children is done by using either the “best interests” standard or the “reasonable parent” standard.

The best interests standard allows guardians to balance the potential benefits of therapy with the risks of such treatment, taking into account the natural history of the disease process, treated or untreated. In contrast, the rational parent standard allows surrogates to make decisions based on their own values as parents, as long as they are reasonable.²⁵ The “reasonableness” of a decision can often be a legal determination.

When parents, as proxy decision makers for their children, act in a way that seems counter to the best interests of their children, physicians are not obligated to follow parental direction. Commonly encountered examples occur when parents decline life-saving treatment for their children on religious grounds. A substantial body of jurisprudence supports medical decision making based on the best interests of the child, rather than on the wishes of the parents: “Parents may be free to become martyrs themselves. But it does not follow that they are free, in identical circumstances, to make martyrs of their children.”²⁶ Clearly, surgeons should do all they can to make decisions in concert with families but are under no obligation, legally and morally, to provide or withhold treatment when they feel it to be in the best interests of young patients unable to provide consent themselves.

Although most children below the statutory age of consent do not have the legal authority to provide informed consent, it has become increasingly common to include children, especially adolescents, in the decision-making process. This has become popularly known as obtaining “assent” to treatment.²⁷ In a 1995 paper, the American Academy of Pediatrics Committee on Bioethics recommended that the concept of informed consent should be altered to one of “informed permission” from parents, and that when appropriate, assent to treatment should be obtained from the child.²⁸ Obtaining assent from a child includes informing the child, in an age-appropriate manner, of

the nature of the illness; explaining the likely course of action, including testing and therapy; and assessing the child's understanding of the situation and willingness to proceed (or refuse) the proposed treatment. In some legal jurisdictions, there is no legal age of consent for medical decision making, and it is left to the physician to decide if a child has the capacity to make medical decisions.

Clearly, the assent process is different for a 16-year-old than for a 9-year-old or a 4-year-old. There is evidence to suggest that the decision-making abilities of children as young as 14 are similar to those of adults in response to hypothetical medical dilemmas.²⁹ As the preceding case illustrates, adolescents may be able to make informed decisions regarding their health care before reaching the age of consent. This can be especially difficult for caregivers when those preferences are to refuse treatment.

6.3.3 End-of-Life Issues

A 13-year-old girl with a left frontal glioblastoma multiforme has undergone two separate resections as well as adjuvant radiation and chemotherapy. She presents with acute left-sided weakness, severe headache, and a computed tomographic (CT) scan showing progression of disease with hemorrhage into tumor that has invaded her contralateral hemisphere. The patient, her family, and caregivers decide on palliative measures only. The child's severe headache and nausea are treated with patient-controlled analgesia and antiemetics. After appropriate supports are put in place, the girl eventually dies comfortably at home, surrounded by family and friends.

The death of a patient is an event pediatric neurosurgeons face more frequently than many other physicians, whether it results from malignant neoplasms, trauma, or complex congenital neurologic disorders. Although there are no published data specific to pediatric neurosurgical patients, evidence in the pediatric critical care and pediatric oncology literature suggests that there are widespread deficiencies in the provision of pediatric palliative care.

Most consensus guidelines regarding end-of-life care see "no ethical distinction between withholding or withdrawal of life-sustaining treatment"³⁰ and suggest that physicians should "aggressively treat pain with analgesic drugs and, when needed, with heavy sedation, even if these treatments hasten death." The attitudes of pediatric neurosurgeons toward the withdrawal of life-sustaining care are not known, but in a survey of pediatric critical care physicians and nurses,^{31–34} none of the physicians surveyed felt that withholding or withdrawing life-sustaining care from dying children was unethical. Despite this, a survey of parents of children who had died of cancer showed that 89% of the children suffered "a lot" or "a great deal" in their last month of life, usually from pain, fatigue, or dyspnea.³⁵ This suggests that a greater awareness of the suffering and subsequent treatment of the suffering of dying children are needed. Pediatric neurosurgeons should play a leading role in ensuring that our patients with terminal illnesses die with the dignity and comfort they deserve.

6.3.4 Research and Children

A study on the transmission of hepatitis B took place at the Willowbrook School (an institution for developmentally challenged

children) in 1966. In the study, new residents at the school were intentionally infected with hepatitis in order to study transmission among residents. At the time of the study, hepatitis B was endemic in the institution, and most residents contracted the virus during their stay. It is unclear what parents were told about the process, and toward the end of the study, it was suggested that children whose parents agreed to allow them to participate were given preferential placement in the school.

The evolution of bioethics in the 20th century occurred largely in response to concerns related to human subjects research. The Nuremberg and Helsinki Codes came in response to Nazi atrocities in the Second World War,⁷ and many credit Henry Beecher's courageous paper on ethics and clinical research,³⁶ which detailed the Willowbrook study highlighted above, with starting the process of ethics review of human subjects research. Today, virtually every university and many hospitals have REBs or IRBs to review research protocols before they start. Many journals require REB or IRB approval as a prerequisite for publication.

Emanuel et al outlined seven requirements for the ethical conduct of human subjects research³⁷:

1. The research must be of value—that is, it has the potential to enhance health or knowledge.
2. It must be conducted such that the results are scientifically valid and methodologically rigorous.
3. Study populations and sites are chosen in a fair way—not based on vulnerability or privilege.
4. There must be a favorable risk–benefit ratio, with risks minimized and the potential for benefit to individuals and knowledge gained by society outweighing risks.
5. The research should be reviewed by unaffiliated individuals with the power to approve, amend, or terminate the research.
6. Participants must provide voluntary informed consent.
7. Subjects should have their privacy respected and have the ability to withdrawal from the trial.

Clinical research using children requires an even higher standard than research using competent adults, given that children are an especially vulnerable population. Although six of the seven requirements outlined by Emanuel et al can be applied to pediatric research, many children, by virtue of their age or capacity, are unable to provide informed consent. Issues of informed consent and pediatric patients have been referred to earlier, but there are distinct differences between consent for medical care, which is presumed to be of benefit to the patient, and consent to participate in clinical research, which may offer only the prospect of benefit and the potential for the assumption of risk without benefit.

Children are considered a potentially vulnerable population in research ethics. Kipnis outlines seven vulnerabilities in pediatric research subjects that should be considered by all investigators³⁸:

1. They commonly lack the capacity to make mature decisions.
2. They are subject to the authority of others.
3. They (and their parents) may be deferential in ways that can mask dissent.
4. Their rights and interests may be socially undervalued.

5. They may have acute medical conditions requiring immediate attention that make informed consent impractical.
6. They may have serious medical conditions that cannot be effectively treated.
7. They (and their parents) may lack access to social benefits such as health care.

Outside the context of clinical research, the concept of informed permission from surrogate decision makers has evolved for making decisions regarding medical treatment. Parental permission for pediatric research is increasingly being thought of as necessary but not sufficient for the ethical conduct of such research.³⁹ In addition to informed permission, the assent of the child involved in the research should be sought, when possible.³⁷ Obtaining assent recognizes and respects the developing autonomy of the child. Assent, however, should be seen as a continuum, based on the developmental level of the child, “ranging from mere affirmation in the youngest child, to the equivalent of the informed consent process in the mature adolescent.”⁴⁰

Current federal regulations in the United States allow IRBs to approve pediatric research if it conforms to one of three categories⁴¹:

1. Studies that offer participating children a prospect of direct benefit
2. Studies that do not offer a prospect of direct benefit but pose only minimal risk
3. Studies that do not offer a prospect of direct benefit and pose a minor increase over minimal risk

Minimal risk is defined as risk for harm or discomfort “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”⁴² Current debate centers on what constitutes a minimal risk or a minor increase over minimal risk, as these could be considered subjective. Much work continues and needs to be done regarding the ethics of clinical research in the pediatric population. In the end, a balance between the need for important clinical research in pediatric neurosurgery and the protection of potentially vulnerable research subjects must be found.

6.4 Surgical Innovation

Historically, novel surgical procedures have developed and been adopted into practice by a process of trial and error, with dissemination among peers through the publication of case reports and series and presentations at specialty meetings. Unlike novel pharmaceutical agents, which must undergo a rigorous process of regulatory review (which almost always involves randomized controlled trials), a new operation can be adopted without any regulatory oversight.

There is widespread acceptance that novel surgical therapies need to undergo a more rigorous validation process before they are adopted into practice by the broader surgical community.⁴³ The use of arthroscopic surgery for osteoarthritis of the knee is an example of a procedure in wide use that has been shown to be no better than medical management when studied in a randomized controlled fashion.⁴⁴

The ethical principles of beneficence and nonmaleficence underpin the argument for more rigorous evaluation of novel

surgical procedures. Even the simplest surgical procedure carries with it the potential risk for harm. If that procedure has not been shown to have a corresponding potential for benefit outweighing the risk for harm, than it is unethical for it to be widely adopted.

In response to these concerns, a group of methodologists and surgical clinicians known as the Balliol Collaboration developed a series of recommendations for the evaluation of surgical innovation, now known as the IDEAL recommendations.⁴⁵ These recommendations outline a five-step process consisting of the following:

1. An innovative idea (I), with a procedure done in selected patients and disseminated through case reports
2. Development (D), involving the planned use of a procedure in a small group of patients, by a selected number of surgeons to refine and modify techniques
3. Exploration (E), involving wider use of the procedure in more centers, with mentoring and the systematic capture of data, including adverse outcomes
4. Assessment (A), involving full evaluation of the novel procedure, ideally through a randomized controlled trial, and finally
5. Long-term study (L), allowing the capture of rare late complications and long-term outcomes. Of note, review by an IRB or an REB is required for steps 2, 3, and 4 and, depending on the nature of the innovation, may need to be sought for step 1.

Although started well before the IDEAL recommendations were published, the Management of Myelomeningocele Study (MOMS) is an excellent example of using rigorous methodology and practice to evaluate the efficacy of a procedure before its acceptance into practice.⁴⁶ Initial results of the fetal repair of MMC showed promise. However, because of concerns about premature adoption of the procedure as an acceptable standard of care, a decision was made by the pediatric neurosurgery community to halt expansion of the procedure to other North American centers and organize a randomized controlled trial. Pediatric neurosurgeons across North America agreed that no further fetal repair would be done outside the three study centers until its efficacy could be proven.

6.4.1 Fetal Surgery

The emergence of fetal intervention in the last two decades as a therapeutic option for lethal and nonlethal conditions diagnosed before delivery requires consideration of overlapping ethical issues. Most important of all is the balance between maternal risk and the benefit to her unborn fetus. Putting aside the psychological well-being of a mother who feels that her child's health has improved, the mother does not derive any direct physical benefit. The question remains whether the mother is able to provide a truly objective informed consent in this situation. This problem was approached in MOMS through multiple sessions in which providers allowed the mother to hear the risks and benefits repeatedly and from different perspectives. A final step was an evaluation of the mother's understanding by a social worker who was not a member of the actual treatment team. Inability to understand the issues presented was sufficient grounds to warrant exclusion from the study.

Dickens and Cook provide an excellent overview of some of the ethical and legal issues in fetal surgery.⁴⁷ These include controversial and as yet unresolved issues, such as whether a fetus has any inherent moral status, the potential conflict between maternal and fetal health, and whether the state should have any interest or say in fetal life.

6.5 Conclusion

Pediatric neurosurgeons encounter ethical and moral dilemmas frequently. An awareness of these issues and the ethical principles that surround them can help neurosurgeons to make decisions regarding the optimal treatment of our most vulnerable patients. This chapter has served as an introduction to the basic concepts of bioethics, with an emphasis on their application to pediatric neurosurgery.

Pearls

- A common misconception regarding bioethics is that there is one “right” answer for a given moral or ethical dilemma. The correct course of action is profoundly influenced by the experience and background of the individuals involved. A bioethical analysis resides in a middle ground between things that seem to be incontrovertibly factual and those that are entirely subjective.
- The “four pillars” of modern bioethics are autonomy, nonmaleficence, beneficence, and justice. Decisions should be guided by these basic goals.
- Children are considered a potentially vulnerable population in research ethics. There are specific vulnerabilities in pediatric research subjects that should be considered by all investigators.

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7 Applications of Cellular Therapy in Pediatric Neurosurgery

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The development of cellular therapy, particularly stem cell (SC) therapy, for the treatment of central nervous system (CNS) disease has progressed rapidly in recent years. Scientists and translational clinicians have targeted SC therapy to broad categories of illness, from inherited metabolic diseases, such as neuronal ceroid lipofuscinosis (NCL), to neoplasms, such as brainstem gliomas. SCs have the potential to revolutionize therapy for previously untreatable CNS diseases. SC therapy, however, is challenged by scientific hurdles as well as by ethical controversy.

SCs have been defined as "...a population of cells capable of indefinite self-renewal that give rise to 'daughter' cells committed to specific differentiation lineages through asymmetrical cell division."¹ The term *stem cell* may refer to tissue derived from embryonic or adult sources, to cells with limited or unlimited potential to divide and replicate, and to cells that are already committed to neuronal, astrocytic, or oligodendrocytic lineages. *Asymmetric cell division* refers to the ability of a cell to produce a copy of itself plus a more differentiated cell, whereas *symmetric division* is the ability of a cell to produce two copies of itself.² Based on the local environment and the presence of various differentiation factors, SCs have the ability to differentiate into any cell type from any of the three germ cell layers. During differentiation, SCs pass through specific, stereotyped stages depending on lineage. For example, during differentiation into a neuron, an embryonic stem cell (ESC) must pass through the following stages: ESC, neuroepithelial cell, neural stem cell/progenitor, and neuron.^{3,4} Generally, as SC differentiates, its ability to self-renew and multiply diminishes.

The use of SCs in clinical translation is in its infancy. Very few human clinical trials are complete, with even fewer of these studying pediatric patients and diseases. This chapter first reviews the various types of SCs and their potential sources of origin for human therapy. We then contrast cellular therapy with strategies using other biological agents. We briefly outline various methods of delivering cellular therapy to the CNS and then review preclinical and, where available, clinical trials of cellular therapy for brain tumors, epilepsy, stroke, lysosomal storage disorders (LSDs), and spinal cord injury. Finally, we address limitations to the use of cellular therapy in children, including ethical considerations.

7.1 Sources of Stem Cells

7.1.1 Embryonic Stem Cells

ESCs are isolated from the inner cell layer of blastocysts that develop approximately 5 to 6 days following fertilization.^{1,5} ESCs are derived from the pre- or peri-implantation embryo, have the ability to undergo undifferentiated proliferation, and are capable of pluripotent differentiation into all three cell layers: ectoderm, mesoderm, and endoderm.⁵ Various ectodermal derivatives of ESCs include dopaminergic neurons⁶⁻⁸ and neural precursors,⁹ whereas mesodermal derivatives include blood vessels.¹⁰

Human ESCs may be retained in vitro for years and cultured with a high yield.^{11,12} They also have the potential for controlled differentiation and subsequent transplantation as neural stem cells (NSCs), astrocytes, or neurons. During normal development, ESCs within the neural plate differentiate based on their reciprocal interactions with surrounding cells and with gradients of morphogenic proteins, including Wnt, Shh, bone morphogenic protein (BMP), and fibroblast growth factors (FGFs).¹³ These biological variables can be used to direct the differentiation of ESC cultures in vitro for therapeutic purposes.

The use of ESCs for human therapy has been restricted because of their neoplastic potential. Because ESCs have the ability to robustly differentiate into all germ cell layers, teratoma formation has been reported in several animal models.¹⁴⁻¹⁶ In another animal model, undifferentiated neuroepithelial cell mitotic activity was found after ESC transplantation.¹⁷

At the time this chapter was written, only 152 ESC lines were eligible under U.S. federal regulations for use in National Institutes of Health (NIH)-funded research.¹⁸ For regulatory, practical, and ethical reasons, the supply of human ESCs is quite limited. Efforts to develop tools for cellular therapy with biological properties similar to those of ESCs have therefore garnered significant scientific attention in recent years.

Somatic Cell Nuclear Transfer

Somatic cell nuclear transfer (SCNT) involves replacement of the nuclear contents of an oocyte, or egg cell, with those of a somatic donor cell.⁵ The engineered cell is then artificially activated in a process analogous to fertilization by sperm and undergoes development. Using this technique, Rideout and colleagues replaced the *Rag2* gene in transplanted SCNT ESCs, producing allogeneic mature B and T cells in rodents with *Rag2* gene deletion, thus restoring their cellular and humoral immunity.¹⁹ In other studies, SCNT ESCs increased hemoglobin A protein levels and decreased polychromasia and anisocytosis in a mouse model of sickle cell anemia.²⁰ This approach may be used in the future to treat patients who have known gene deletions or mutations with SCNT ESCs containing normal copies of the specific missing or mutated gene. At the time of this writing, however, SCNT ESCs have not yet been established using a human ovum.

Transcription-Induced Pluripotency

Expression of genes normally active in ESCs can induce adult fibroblasts to enter a developmental state similar to that of ESCs.²¹ The four genes necessary to create these "induced pluripotent stem cells" (iPSCs) include *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*.²¹ The creation of iPSCs with fibroblasts from nonhuman primates,²² and soon thereafter from humans,²³ ignited intense public interest in these cells as an ethically benign alternative to ESCs for human clinical therapy.²⁴

Like ESCs, iPSCs demonstrate germline transmission of their genetic material. Unfortunately, as with other ESCs, a

substantial number of the offspring of transplanted animals develop teratomas, possibly because of the activation of *c-myc*.²³ This finding may limit the use of iPSCs in human therapy.

7.1.2 Adult Stem Cells

Adult stem cells (ASCs, sometimes also referred to as somatic stem cells) are multipotent progenitor cells, in distinction to pluripotent ESCs.⁵ ASCs are isolated from the brain, bone marrow, or other organ systems of humans or animals and can be cultured and expanded *in vitro*.^{25,26} Although they are referred to as “adult” SCs, the source of these cells in many cases is organ-specific fetal tissue. ASCs differentiate into cells of other tissue origin only via the process of “transdifferentiation.”^{27,28} ASCs grown in the presence of Lin28, Nanog, Sox2, and Oct4 exhibit many characteristics of ESCs, including pluripotency.²⁹ Such modified ASCs could be extracted from, modified, and reimplanted into the same patient, potentially avoiding immunologic complications and the ethical concerns arising from the use of ESCs in human therapy.

7.1.3 Primary Neural Cells

Primary neural cells (PNCs) are obtained from fetal cerebral tissue. PNCs cultured from human fetal mesencephalon were used in two clinical trials for the treatment of Parkinson disease (PD).^{30,31} Advantages of PNCs include a low risk for tumor formation and predictable phenotype.¹³ However, because they are already differentiated, PNCs largely lack the ability to expand in culture, significantly limiting their human therapeutic potential.

7.1.4 Neural Stem Cells

NSCs may be of embryonic or somatic origin.³² NSCs proliferate within the subventricular zone (SVZ) of mammals, follow a rostral migratory stream, and form new neurons within the olfactory bulb.^{33–35} NSCs are also responsible for the generation of new dentate gyrus granule cells in the hippocampus.^{36,37} Frequently, the terms *neural stem cell* (NSC) and *neural progenitor cell* (NPC) are used interchangeably. Unlike NSCs, however, NPCs are limited in their ability to self-replicate and typically do not form neurospheres.³⁸

Essentially, all NSCs derive from cells that produce glial fibrillary acidic protein (GFAP)³⁹ and give rise to neurons, glia, and oligodendrocytes.⁴⁰ A variety of trophic factors direct NSC differentiation into these specific cell lineages. Platelet-derived growth factor (PDGF),⁴¹ transforming growth factor- β_1 (TGF- β_1),⁴² neurogenin, mammalian AS-C homologue (MASH), and helix loop helix factor (HLH-f)⁴³ facilitate differentiation into neurons. BMP⁴² and leukemia inhibitory factor facilitate, while Noggin (a BMP inhibitor) interrupts, differentiation into astrocytes.^{43,44} Finally, insulin-like growth factor-1 (IGF-1) promotes oligodendrocytic differentiation.⁴² The expression of various transcription factors can similarly influence NSC differentiation.² Environmental factors also influence differentiation into CNS cell subtypes.^{45,46} One example is the differentiation of SCs into dopamine-producing neurons necessary for the treatment of PD.^{26,47}

7.1.5 Bone Marrow–Derived and Umbilical Cord Blood Stem Cells

Bone marrow–derived mesenchymal stem cells (BMSCs) are multipotent cells capable of re-creating lineages independent of the hematopoietic system. The key limitation to using BMSCs for treating CNS diseases is technical difficulty in inducing their transdifferentiation. However, BMSCs have the capability to differentiate into all three germ cell layers⁴⁸ and have been transdifferentiated into NSCs.^{49,50} BMSCs have been shown to cross the blood–brain barrier (BBB), thereby offering the potential for CNS vascular repair following stroke⁵¹ and remyelination following white matter injury.⁵² BMSCs may also have a neuroprotective effect, enhancing host neuronal survival after injury by releasing neurotrophic growth factors.⁵³

Umbilical cord blood (UCB) is also rich in mesenchymal SCs.⁵⁴ Engraftment rates may be higher for UCB than for BMSCs in treating Hurler syndrome,⁵⁵ although such differences are not consistent.⁵⁶ Advantages of UCB include low incidence of graft-versus-host disease, low risk for transmitting disease, rapid availability, and possibly a better graft rate than other hematopoietic SC sources.⁵⁷

Common sources of SCs are reviewed in ► Table 7.1.

7.2 Contrast to other Biological Agent Strategies

Cellular therapy follows a long line of rationally designed and targeted therapies for incurable and previously untreatable neurodegenerative diseases. This era of designed therapies began with the development of L-3,4-dihydroxyphenylalanine (L-DOPA) for the treatment of PD.⁵⁸ Although L-DOPA relieved some of the symptoms resulting from the degeneration of nigral dopaminergic neurons in patients with PD, it did not interfere with the inexorable underlying pathologic process. Subsequent developments in neurodegenerative disease therapy reflect both an attempt to more directly interrupt disease pathophysiology and growth in basic biological expertise in protein chemistry, genetics, and ultimately cellular therapy. Development of novel therapies for the incurable, inherited LSDs provides an example of this progress. The LSDs are characterized by the deficiency of an enzyme or enzymes that results in the accumulation of pathologic material in lysosomes, ultimately causing neuronal death and CNS dysfunction.

7.2.1 Enzyme Replacement Therapy

Intravenous (IV) enzyme replacement therapy (ERT) is the principal approach for treating many inherited enzyme deficiency diseases, including the LSDs⁵⁹ mucopolysaccharidosis (MPS) VI (Maroteaux-Lamy syndrome),⁶⁰ glycogen storage disease type 2 (Pompe disease),⁶¹ MPS I (Hurler syndrome),⁶² α -galactosidase A deficiency (Fabry disease), and glucocerebrosidase deficiency (Gaucher disease).⁶³

Hunter syndrome is caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase. IV infusion of idursulfase for Hunter syndrome has resulted in multiple somatic improvements, such as increased mobility, decreased hepatomegaly, and decreased respiratory infections.⁵⁹ IV delivery of idursulfase has not,

Table 7.1 Summary of cell types

Cell type	Donor source	Advantages	Disadvantages
Embryonic stem cells (ESCs)	Embryo	Undifferentiated proliferation Capable of differentiation into all three germ cell layers Long-term in vitro storage	Neoplastic potential Difficulty directing differentiation in vitro
Somatic cell nuclear transfer embryonic stem cells (SCNT ESCs)	Oocytes and somatic donor cells	Differentiation potential similar to that of ESCs	Efficacy not yet shown in humans
Induced pluripotent stem cells (iPSCs)	Adult fibroblasts plus specific genes	Avoids ethical issues of ESCs Differentiation potential similar to that of ESCs	Neoplastic potential
Adult stem cells (ASCs)	Developed organs (e.g., brain, bone marrow)	No immunocompatibility or ethical issues for autograft Expandable in vitro Safe	Restricted neural differentiation potential Questionable functional differentiation
Primary neural cells (PNCs)	Fetal cerebral tissue (mesencephalon)	Low neoplastic potential Predictable phenotype	Unable to expand in vitro Require stage-specific embryonic source Limited differentiation potential
Neural stem cells (NSCs)/ Neural progenitor cells (NPCs)	Embryo Subventricular zone of adults	Able to differentiate into neurons, glia, and oligodendrocytes Long-term vitro storage and expansion	Limited sources
Bone marrow–derived stem cells (BMSCs)	Bone marrow	Capable of differentiation into all three germ cell layers Crosses the blood–brain barrier Neuroprotective effects	Difficulty with transdifferentiation into NSCs

Source: Adapted from Guillaume DJ, Zhang SC. Neuronal replacement by transplantation. In: Bottenstein J, ed. *Neural Stem Cells: Development and Transplantation*. Norwell, MA: Kluwer Academic Publishers; 2003:309.

however, resulted in similar improvements in CNS function because of the relative failure of IV therapy to deliver replacement enzyme to the CNS.⁶⁴ In many disease states, ERT is completely ineffective because of BBB obstruction of CNS penetration.⁶³

7.2.2 Viral Vector Gene Therapy

The NCLs are examples of diseases untreatable with peripheral ERT. Late infantile NCL, an autosomal-recessive lysosomal storage disorder caused by mutation of the *CLN2* gene, results in profound deficiency of the lysosomal storage enzyme tripeptidyl peptidase 1 (TPP1), neuronal loss, progressive neurologic decline, and death.⁶⁵ Adeno-associated viruses (AAVs) can transfer human *CLN2* cDNA to genetically deficient cells in vitro and in rodent and primate animal models.⁶⁶ Gene transfer therapy increased levels of the deficient enzyme, TPP1, in the striatum, substantia nigra, frontal cerebral cortex, and thalamus of the injected hemisphere, and in the contralateral frontal cerebral cortex. Another group found similar results in an animal model of a related disorder, infantile NCL.⁶⁷

In a study of 10 children with late infantile NCL, AAV vector gene therapy may have slowed disease-related brain atrophy and neurologic deterioration compared with control subjects.⁶⁵ Given the low numbers of patients in this study, no difference in outcomes was statistically significant. Several adverse events were noted, including the death of one patient secondary to postoperative status epilepticus, as well as development of a humoral immunoresponse to the vector in four patients.

Gene replacement therapy is also being tested in animal models of other LSDs, including MPS VII (Sly syndrome) and MPS IIIB (Sanfilippo syndrome). In rodent models of MPS VII, direct intracerebral injection of the AAV2 vector, transplantation of retrovirus-transduced fibroblasts, and transplantation of adenovirus-transfected amniotic epithelial cells all reduced pathologic lysosomal storage.^{68–70} A similar viral gene therapy approach has been effective in a rodent model of MPS IIIB.⁷¹ This viral therapy strategy may be improved by using organ-specific NPCs.^{72,73}

Viral gene therapy for neurodegenerative disease faces a number of ongoing challenges. Individual viral vectors and genetic payloads must be designed for every genetic disease and disease variant. Each of these vectors must undergo extensive safety testing and regulatory approval.⁷⁴ The efficiency of transfection may be limited in many cases, and more efficient viruses may also pose a higher risk for associated pathologic inflammatory responses.⁷⁵ Finally, although they may spread by transfection, viruses have no inherent migratory potential. Thus, the delivery of the therapeutic agent to the entire expanse of the human nervous system in LSD is a daunting challenge and would likely require vascular delivery across the BBB.

7.3 Clinical Applications of Stem Cell Therapy

The inherent properties of SCs may prove advantageous in overcoming the daunting challenges of treating CNS neuro-

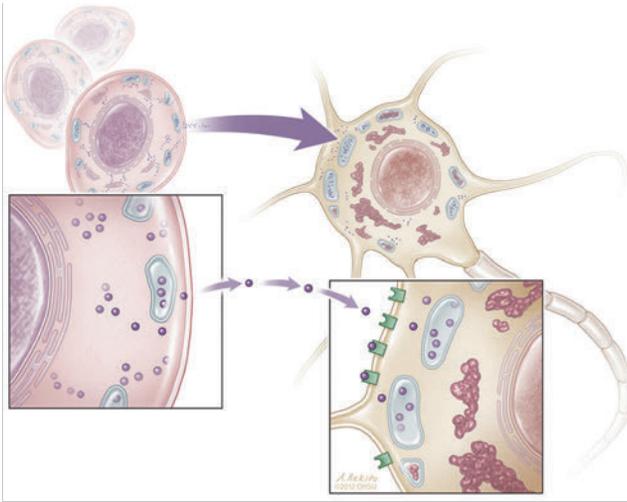


Fig. 7.1 Intercellular transfer of deficient enzymes from an intracerebrally transplanted neural stem cell to a neuron in a process known as metabolic cross-correction. Stem cells secrete active enzymes, which are then taken up by receptor-mediated endocytosis into enzyme-deficient neurons and transported to lysosomes, reducing precursor accumulation, normalizing lysosomal function, and protecting neurons from degeneration.¹³

degenerative disease. For example, implanted lineage-specific, or adult, SCs may survive indefinitely in the host environment, self-replicate or expand, and migrate significant distances within the CNS.^{76,77}

For LSDs and other enzyme deficiency diseases related to an isolated genetic defect, SCs may be used in a cross-correction strategy. In this circumstance, transplanted, genetically normal SCs produce and secrete the missing protein, which diffuses locally and supplies the genetically deficient host cells (► Fig. 7.1).¹³

NSCs are capable of differentiating in situ into the three major cell lineages of the mature CNS: neurons, astrocytes, and oligodendroglia⁷⁸ (► Fig. 7.2). The most sophisticated and technically challenging use of SC therapy for CNS diseases will be replacement of damaged neuronal circuits and glial architecture based on these regenerative and pluripotent properties. Cross-correction models, however, do not require lineage-specific differentiation or circuitry repair.

7.3.1 Cellular Delivery

Various methods for delivery of SCs to their therapeutic target have been employed, including IV, intra-arterial (IA), and direct surgical implantation. IV administration of SCs is less invasive than either IA or direct surgical implantation, but delivery of cells to the CNS is significantly hindered by a pulmonary first-pass effect,⁷⁹ with only approximately 4% of cells entering the brain.⁸⁰ Up to 21% of cells injected into the internal carotid artery enter the brain,⁸¹ but this technique may be complicated by the occurrence of microemboli.⁸² Direct intracerebral transplantation followed by intraventricular and IV transplantation results in the greatest number of SCs at the site of a CNS lesion.⁸³ However, functional recovery does not necessarily correlate with the absolute number of viable transplanted cells into the targeted area.⁸⁴

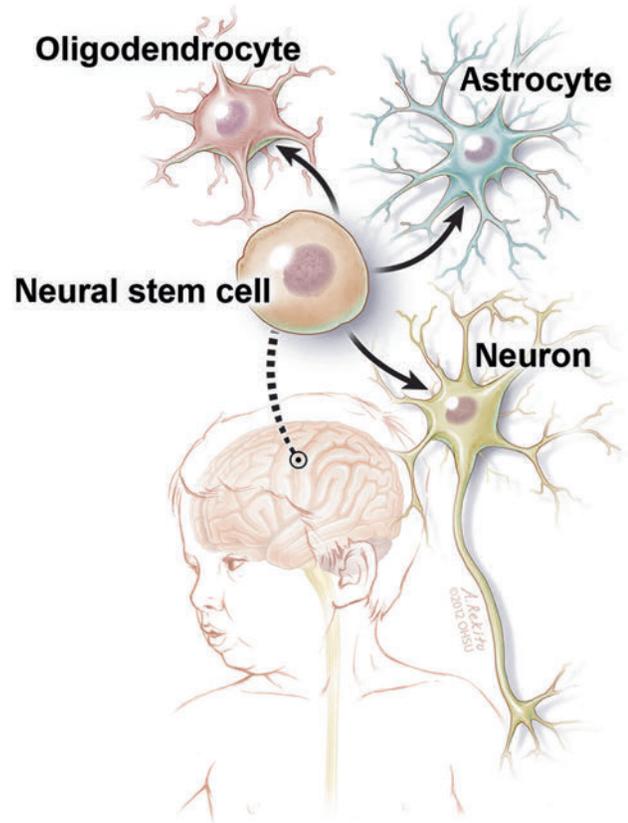


Fig. 7.2 Schematic diagram of an intracerebrally transplanted neural stem cell's capability to differentiate into an oligodendrocyte, astrocyte, or neuron.

Implanted SCs have the ability to improve neurologic outcomes without crossing the BBB. In several preclinical stroke models, neurologic function improved despite that fact that few or no SCs were found in the brain.^{80,85} This is likely due to the ability of NSCs to counteract inflammatory cytokines, toxic metabolites, free radicals, and excitotoxins released systemically after an insult.⁸⁶ NSCs also produce multiple protective factors such as glial cell line-derived neurotrophic factor (GDNF), which may contribute to rescuing dopaminergic neurons in PD¹ and improving functional outcomes after stroke,⁸⁷ as well as glial and neural growth factors, such as neurotrophin-3 (NT-3) and ErbB-2, respectively.^{88,89} Other neuroprotective factors enhanced by NSCs include fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), bone-derived neurotrophic factor (BDNF), nerve growth factor, and ciliary neurotrophic factor.^{87,90}

7.3.2 Disease States

Ischemia

Cerebral ischemia from moyamoya disease, genetic disorders, and perinatal thromboembolic disease results in profound morbidity in the pediatric population. Cerebral ischemia triggers the proliferation of NPCs in the SVZ^{91,92} and dentate gyrus. NPCs migrate to areas of focal ischemia in rodent models.^{93,94} SVZ cells may have the capacity to regenerate some striatal

neurons following ischemia.⁹⁵ Migration of NSCs to the site of ischemic injury is activated by erythropoietin.^{93,96,97} Epidermal growth factor receptor (EGFR) levels in the SVZ increase following cerebral ischemia, while infusion of EGF into ischemic brain increases the number of EGFR-positive neuroblast precursors,⁹⁵ which migrate into the striatum and cerebral cortex following ischemic insults to those regions.^{93,98} Although the therapeutic implications of these findings remain unclear, it appears that SVZ and other stem and progenitor cells demonstrate tropism toward sites of CNS injury.

For neuronal circuit repair after stroke, implanted SCs must migrate to appropriate targets and also differentiate into appropriate cell types. In a rodent ischemia model, implanted ESC-derived NPCs differentiated into neurons and glia with electrophysiologic function.⁹⁹ Similarly, transplanted NSCs in a gerbil model of ischemia yielded NeuN-positive neurons and glial fibrillary acidic protein (GFAP)-positive glia, grew synaptic connections between host and graft tissue, and improved neurologic function.¹⁰⁰ After intraventricular injection, NSCs in a mouse model of neonatal hypoxic-ischemic encephalopathy migrated to the site of ischemic injury and differentiated into neurons, resulting in improved memory and learning compared to controls 8 months after transplantation.¹⁰¹ Intracerebral transplantation of NSCs in a rodent model of cerebral palsy (CP) yielded a 5% population of NSC-derived neurons in the infarction cavity.¹⁰² At the time of this writing, there were no published clinical trials of SC therapy for CP; however, two clinical trials have been completed, and three trials are currently recruiting patients.¹⁰³ When the NSC neurons were transduced with a retroviral neurotrophin (NT-3) before transplantation, the proportion of NSC-derived neurons in the infarction cavity increased to 20% and in the penumbra to 80%, raising the possibility that these therapies interact synergistically. In other studies, IA^{104,105} or IV⁸⁴ SC injection to treat stroke has also improved neurologic recovery.⁸⁴

Human studies support the potential of SC therapy for the treatment cerebrovascular accidents (CVAs). Human neuronal cells implanted into 14 adult patients with ischemic or hemorrhagic CVA were associated with improved activities of daily living and memory compared to baseline, but not compared to nonimplanted controls.¹⁰⁶ No significant change was noted in European Stroke Scale motor score. In one patient, who expired 27 months after transplantation, human neuronal cells were found adjacent to the lacunar infarct.¹⁰⁷ Another clinical study of intracranial implantation of fetal porcine cells for stroke therapy was terminated by the U.S. Food and Drug Administration (FDA) after enrolling only five patients because of the occurrence of adverse events, including worsened motor deficits and seizure onset following transplantation.¹⁰⁸

SCs may play different roles in stroke therapy depending on the timing and route of administration. SC administration very early after ischemic stroke may provide neuroprotection of salvageable penumbra by increasing neuronal proliferation and abating edema,^{102,109} although the proportion of SCs surviving transplantation is relatively low.^{76,110} By contrast, SCs administered peripherally 21 days after ischemic injury survive in greater numbers and differentiate via neuronal and glial lineages within injured brain.¹¹¹

Tumors

Currently, the most common application of SC therapy in children is high-dose chemotherapy (bone marrow-ablative) with autologous hematopoietic SC transplant rescue as a salvage therapy for recurrent or high-risk brain tumors. The most common source of SCs is peripheral blood, followed by bone marrow. This treatment has been used in a variety of neoplasms, including medulloblastoma, malignant glioma,¹¹² ependymoma, germ cell tumors, and atypical rhabdoid teratoid tumors.¹¹³ Responses are variable (0 to 75% long-term survival) and often at the price of substantial toxicity, including death in up to 33%, mucositis, neutropenia, and renal and hepatic failure.¹¹³ There are currently approximately 40 registered SC-based clinical trials worldwide for pediatric brain tumors, which will continue to define the safety and efficacy of this treatment strategy over time.¹¹⁴

Brainstem gliomas and supratentorial malignant gliomas constitute approximately 15%¹¹⁵ and up to 10%,¹¹⁶ respectively, of pediatric brain tumors. Neural SCs appear to have a high affinity, or tropism, for brain tumor tissue, making them ideal vehicles for the introduction of therapeutic enzymes and chemotherapy.^{113,114} Bone marrow-, adipose tissue-, and umbilical cord-derived SCs all show tropism for brain tumor tissue, with comparable rates of SC survival and percentage of migratory cells.¹¹⁵ Tumors attract SCs via the secretion of numerous chemoattractant factors, including cytokines, VEGF, stromal cell-derived factor-1 (SDF-1), NT-3, TGF- β_1 , and interleukin-8 (IL-8).^{114,117}

Interleukin-4 (IL-4) cDNA delivered via SCs in a rodent model of malignant glioma resulted in tumor regression, as determined by magnetic resonance (MR) imaging, and significantly improved survival.¹¹⁸ In this study, treatment with unaltered NSCs alone also provided a degree of intrinsic antitumor activity. In another study, BMSCs expressing interferon- γ (IFN- γ) increased survival in a model of supratentorial malignant glioma.⁷⁷

Mesenchymal SCs (MSCs) have also successfully delivered prodrug converting enzymes in animal models of brainstem glioma. As a proof of concept, human NSCs engineered to express cytosine deaminase, a prodrug enzyme, and IFN- γ , an antiangiogenic and immune response enhancer, migrated, increased tumor cell apoptosis, and substantially reduced tumor volume in a model of brainstem glioma.¹¹⁵ Human adipose tissue-derived MSCs genetically altered to convert the prodrug of irinotecan, a topoisomerase-1 inhibitor, into the active form significantly extended the survival of rats treated with both the engineered MSCs and irinotecan.¹¹⁹ This strategy is also being tested in human clinical trials. Genetically modified NSCs expressing an enzyme for the conversion of 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU) are being evaluated for the treatment of recurrent high-grade gliomas.¹²⁰

NSCs also show substantial tropism toward medulloblastoma. Even when injected in the contralateral hemisphere in an animal model, human NSCs engineered to convert systemic 5-FC to 5-FU reduced the size of medulloblastoma tumors by 76%.¹²¹ In another model, human NSCs engineered to convert irinotecan to its active form reduced the growth rate of cerebellar tumors.¹²²

Lysosomal Storage Disorders

The LSDs are a class of over 40 disorders,¹²³ each defined by "... a specific inherited enzyme deficiency that leads to accumulation of complex macromolecules, such as sphingolipids, glycogen, mucopolysaccharides, and glycoproteins in lysosome[s]," ultimately resulting in neuronal death.⁶⁴ Many of the LSDs have their most devastating effects on the CNS. Because of this, the transmission of peripherally delivered therapies, such as enzyme replacement, across the BBB has posed a significant impediment to therapy. For many LSDs, which are often severely morbid or fatal, there is no effective treatment. SC therapy for LSD offers the potential to deliver replacement enzymes in a sustainable fashion within the CNS by using a cross-correction model.

Intraventricular delivery of enzyme, although technically challenging, can positively impact some LSDs. In rodent models of the GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease), intraventricular injection of recombinant human HexA (Om4HexA) with a high mannose-6-phosphate (M6P)-type-N-glycan content reduced levels of sphingolipids, GM2, and asialo-GM2 (GA2) in brain parenchyma and improved both motor function and survival.¹²⁴

SCs may provide continuous and potentially durable enzyme replacement for LSDs. To date, however, the clinical benefits of SC therapy for LSD have been mixed, and success in preclinical models has not necessarily translated to patients. In a rodent model of Niemann-Pick disease, NSCs implanted into the cerebellum increased survival but did not affect weight loss or neurologic function.¹²⁵ A number of animal studies in which multiple treatment methods were used in a single animal, such as BMSC transplantation and ERT, have shown outcomes superior to those obtained when either therapy was used individually.¹²⁶ Multimodality therapy may also prove useful in human patients.

MSCs delivered to 12 patients with metachromatic leukodystrophy or Hurler syndrome did not improve cognitive or physical development.¹²⁷ UCB transplantation in 25 infants with Krabbe disease improved neurocognitive function and development in those patients who were asymptomatic at the time of transplant.¹²⁸ Similar results were found after UCB for X-linked adrenoleukodystrophy (X-ALD).¹²⁹ Hematopoietic SC transplantation is therefore currently advised for use only in asymptomatic patients, creating a premium for the early perinatal diagnosis of inborn errors of metabolism.⁵⁷

Intracerebral transplantation of human NSCs in a rodent knockout model of infantile NCL resulted in SC engraftment, migration, production of the missing palmitoyl-protein thioesterase 1 (PPT1) enzyme, reduced burden of autofluorescent material, and neuronal preservation in cortex and hippocampus.⁷⁸ Based on these results, a Phase I trial of intracerebral transplantation of human NSCs for infantile NCL and late infantile NCL was recently completed. This study utilized multiple intracerebral and bilateral intraventricular surgical implantations (► Fig. 7.3) of very high volumes of SC suspension, with a total dose of SC delivery unprecedented in previous human therapy (up to 1 billion cells per patient). The trial also represented the first human treatment with a purified and characterized NSC, the first human CNS implantation of a purified SC population, and the first surgical CNS transplantation carried out in chil-

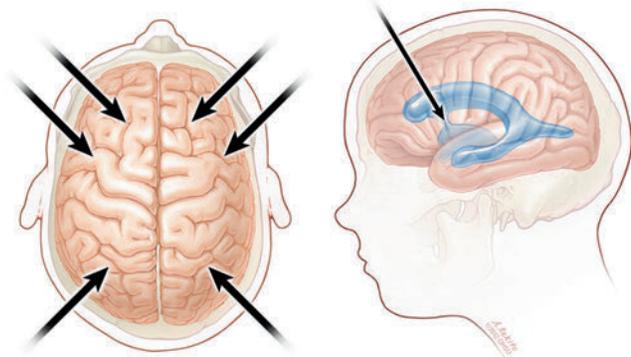


Fig. 7.3 Transplantation of neural stem cells into six intraparenchymal supratentorial sites and bilateral frontal intraventricular sites.

dren.^{130,131} Six children underwent transplantation and were treated with 1 year of immunosuppression. No surgical, SC-related, or immunosuppressive toxicity was observed, and human leukocyte antigen (HLA) antigenic evidence suggested successful engraftment and migration more than 2 years after transplantation and well after the cessation of immunosuppression. The study was not powered to assess efficacy.¹³⁰

Traumatic Brain Injury

Traumatic brain injury is responsible for nearly 500,000 emergency department visits each year by children ages 0 to 14 years.¹³² Mortality and morbidity from severe traumatic brain injury have not improved dramatically over the past 30 years, suggesting the need for novel treatment strategies for neuroprotection after primary brain injury and for neuro-restoration.^{133,134} SC therapy has the potential to deliver these benefits to patients with traumatic brain injury.

Injured brain parenchyma expresses an abundance of inflammatory mediators, creating a hostile host environment for transplanted SCs. Implanted SC viability correlates with the degree of injury.¹³⁵ As in stroke, SC administration is most likely optimal immediately following the injury, before the peak inflammatory response, or after the acute inflammatory process has subsided.⁸²

Bone marrow-derived SCs administered intracerebrally,¹³⁶ IV,^{50,137} or IA¹³⁸ after traumatic brain injury all survived for up to 3 months and migrated to the injury site. NSCs have also been found to migrate to injury sites and are associated with improved neurologic function, surviving up to 14 months.^{82,139} UCB administered after traumatic brain injury contains SCs that differentiate into neurons and astrocytes and result in improved function.¹⁴⁰

In a preliminary study, 10 children with severe traumatic brain injury received IV autologous bone marrow-derived mononuclear cells within 48 hours of injury.¹⁴¹ This feasibility study found no evidence of treatment-related CNS or systemic toxicity but was not designed to assess neurologic or cognitive functioning.

Epilepsy

An increasing amount of preclinical research has focused on using NSCs to treat mesial temporal lobe epilepsy and, to a lesser degree, epilepsy related to cortical dysplasia. The microenvironment of the epileptogenic hippocampus is favorable to the implantation and integration of SCs.¹⁴² Lack of inhibition at the dentate hilus allows the propagation of ictal discharges from the entorhinal cortex to the hippocampus and subsequently the rest of the brain.¹⁴³ One strategy used for the treatment of refractory epilepsy is therefore transplantation of inhibitory NSCs.¹⁴⁴ The dentate gyrus may be the most appropriate target for inhibitory precursor transplantation. Other treatment strategies using SCs for epilepsy include promotion of surround inhibition and neuronal replacement.¹⁴⁵

Transplanted SCs require differentiation of NSCs into inhibitory neurons—for example, those utilizing γ -amino butyric acid (GABA) neurotransmission—to cause mesial temporal inhibition. NSCs implanted into the dentate gyri of rats produce GABA-ergic cells, raise seizure thresholds, and shorten seizure duration.¹⁴⁶ Transplanted embryonic medial ganglionic eminence cells engraft and migrate in large proportions to the hippocampus, striatum, and neocortex in animal models of partial and generalized epilepsy, with prolonged survival.^{147–150} Transplanted cells also influence host neuronal circuitry by increasing levels of synaptic inhibition in neocortical pyramidal neurons.¹⁴⁷ Loss of inhibitory interneurons likely also plays an important role in the pathogenesis of cortical dysplasia, which may represent a potential target for NSC-derived inhibitory neuron transplantation.^{151,152}

Cellular therapy could also reduce seizures in mesial temporal lobe epilepsy by replacing dysfunctional or damaged neurons. NPCs implanted into the cerebral cortex and hippocampus of rats develop projections to the host thalamus and contralateral hippocampus, generate action potentials, and harbor N-methyl-D-aspartate (NMDA)-mediated excitatory and GABA-mediated inhibitory postsynaptic currents.^{153,154}

Spinal Cord Injury

Like the brain, the zone adjacent to the spinal cord ependymal lining is a key site in for NSC formation and proliferation after injury.^{155,156} The host environment at the site of spinal cord injury is important to potentiate SC-induced recovery. Following the clearance of necrotic debris, gliotic scarring inhibits the regeneration of severed axons.¹⁵⁷ Implantation of selected macrophages may play a role in preventing a glial scar, clearing cellular debris, and promoting the migration of endogenous SCs to the site of injury.¹⁵⁸ Recovery of motor function in an animal model is significantly increased when SC transplants and neurotrophins are administered 2 to 4 weeks following spinal cord transection compared to those administered more acutely, in the presence of deleterious, acute inflammatory responses to injury,¹⁵⁹ including such mediators as tumor necrosis factor- α (TNF- α), IFN- γ , and IL- β ₁.¹⁶⁰

In animal models, direct implantation of SC into the injured spinal cord dramatically improves function.^{161,162} NSCs engrafted into the injured cord tend to stay confined to the white

matter and differentiate into glial cells,¹⁶³ particularly oligodendrocytes that form myelin.¹⁶⁴ Nevertheless, those NSCs that differentiate into astrocytes¹⁶⁵ and neurons¹⁶⁶ also have the potential to improve neurological function. Implantation of UCB into the injured spinal cord has also produced myelin¹⁶⁷ and improved neurological function.¹⁶⁸

In a Phase I clinical trial,¹⁶⁹ the injection of autologous macrophages into the spinal cords of eight patients with complete spinal cord injury was associated with recovery in three patients from American Spinal Injury Association Impairment Scale grade A to grade C. Phase II studies are currently under way utilizing this technique.¹⁷⁰ Patients with both subacute and chronic spinal cord injury treated with BMSCs showed modest functional improvements, particularly when cells were injected into the vertebral artery.¹⁷¹ PNCs of fetal origin were directly injected at the site of injury in patients with postinjury syringomyelia without adverse events and with MR imaging correlates of successful engraftment.¹⁷²

7.4 Challenges to Cellular Therapy

7.4.1 Biological Challenges

Immunocompatibility

ESCs differ genetically from recipients but express little HLA class I and no class II.¹⁷³ As ESCs differentiate, class I major histocompatibility complex is upregulated, so that immunosuppressant therapy is required after transplantation.¹⁷⁴ Alternatively, it may be possible by using nuclear transfer or other techniques to create donor ESCs genetically identical to the recipient.^{175,176} The use of immune-inert, semipermeable capsules to house SCs may also promote immunocompatibility and protect SCs from attack by inflammatory modulators resulting from direct cerebral implantation.¹³¹

The proper dose, timing, and duration of immunosuppression after CNS SC transplantation are controversial, especially given the medical fragility of the population of patients for whom SC therapy is currently being explored. In two studies of transplantation of human fetal mesencephalic tissue for PD, one study used immunosuppression and the other did not.^{30,31} Grafted cells were present on postmortem histology from patients in both studies, although an activated macrophage marker (CD45) was increased around SC graft injection sites in nonimmunosuppressed patients.³⁰ In a Phase I trial of human NSC transplantation for NCL, patients were treated with immunosuppression just before and for 1 year after implantation. Frequent medication adjustments were required because of the interaction of anticonvulsant and immunosuppressant drugs, but there were no obvious additional adverse effects. Evidence for persistent engraftment was present in two of three postmortem examinations, in one case more than 2 years after transplantation.¹³⁰ In a single patient with stroke in whom human neuronal cells derived from a teratocarcinoma line were implanted and who received peritransplantation immunosuppression for 9 weeks, the implanted neurons survived for more than 2 years.¹⁰⁷

Neoplastic Potential

ESCs have many similarities to neoplastic cells, including the ability to undergo unlimited, undifferentiated proliferation and to form tumors in animal models of PD.^{15,16} ESCs readily differentiate into all three germ layers and have a propensity to form teratomas. Cell overgrowth^{14,17} and metastatic retinoblastoma formation have also been observed in animal models.¹⁷⁷ To reduce their oncologic potential, ESCs must be used in lineage-specific, differentiated form, such as NSCs. However, brain tumor formation was reported in a human patient 4 years following implantation of fetal NSCs.¹⁷⁸ Pluripotent SCs may be sorted according to their identifying cell surface proteins¹³ or by leveraging cell type-specific transcription factors.¹⁷⁹

Other Biological Obstacles

Scientists and clinicians must overcome several additional obstacles before SC therapy can be widely used in the treatment of pediatric neurologic disorders. First, there is currently a lack of clinical markers that specifically identify transplanted NSCs in order to distinguish them from other progenitor or differentiated host cells.^{1,2} Second, therapeutic strategies must mitigate host factors. For example, direct intracerebral implantation may affect the viability and functionality of SCs because of the creation of a hostile inflammatory microenvironment.^{30,31,106,108,130} The underlying disease state may additionally result in gliosis or vacuolization that can adversely affect engraftment, migration, or the function of transplanted SCs. Third, in many disorders, particularly developmentally relevant disorders in childhood, outcomes assessment may be confounded by a lack of appropriate and validated instruments. For example, most validated measures of neurocognition require intact visual and motor functional skills, which are often damaged early (e.g., in LSDs).¹³¹ Fourth, it is difficult to track the location and assess the viability of implanted SCs in human patients. Guzman and colleagues used iron nanoparticles to successfully trace migration patterns as assessed by MR imaging and histology.¹⁸⁰ Notably, these iron nanoparticles did not affect cellular migration, survival, differentiation, or electrophysiologic characteristics. This technology has the potential to identify single cells.¹⁸¹ Others have successfully employed MR spectroscopy¹⁸² and positron emission tomography (PET)^{183,184} to identify NPCs in humans. Engineering of SCs to facilitate *in vivo* imaging, however, creates additional regulatory hurdles for their use in human trials.

7.4.2 Regulatory and Ethical Challenges

The regulatory issues surrounding SC transplantation are complex and continue to evolve. In the United States, the FDA oversees the use of SCs and other biological therapeutics in human patients. Because they are human cells that are highly processed and “utilized for other than their normal function,”^{185,186} SCs must conform to both Section 351 regarding biological products¹⁸⁷ and Section 361 regarding human cells and associated products¹⁸⁸ of the Public Health Service Act.¹⁸⁵ The U.S. Code of Federal Regulations (CFR) Part 1271 details the regulation of “human cells, tissues, and cellular and tissue-based prod-

ucts.”¹⁸⁶ Generally, this code was designed to “create a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps) and to establish donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps.”¹⁸⁶ Thus, the regulatory standards and checks for the manufacturing of biological material for human use are stringent and expensive.¹⁸⁵

SC research faces additional serious challenges related to ethical concerns about the creation and use of human embryonic and other cellular tissue. Both sides in this debate cite concern regarding the value of human life as a motivating factor. Proponents of SC therapy identify concern for patients with severe or fatal, untreatable nervous system diseases as a factor justifying this work. Opponents cite concern that embryonic tissue, representing human life, will be arbitrarily created or destroyed for the purposes of SC therapy. In both cases, sincerely held views deserve the attention and respect of the medical and scientific communities.¹⁸⁹

The ethical attention of the public and press has focused to a large degree on ESC transplantation.^{190,191} In many cases, however, lineage-specific, or “adult,” SCs are actually sourced from fetal tissue. As discussed previously, SCNT and iPSC technology may in future provide a relatively ethically neutral source of human SCs for therapeutic purposes.

The public focus of attention on the ethics of ESC transplantation has diverted necessary attention from a number of other important considerations: Who should own the intellectual property and biological material rights for cells necessary for human therapy? Is the use of “sham” surgery in human clinical trials of cellular transplantation ethical?³¹ What are the boundaries for the appropriate use of complex and expensive transplantation therapy (particularly in cases in which such therapy may be only palliative)? How can we guard the interests of children and neurocognitively disabled patients enrolled in trials of SC therapy, without entirely denying their access to such therapies and preventing progress in the treatment of their diseases? Because of these and other questions, progress in human SC therapy must occur within the bounds of careful and public regulatory oversight and ethical guidelines.¹⁸⁹

7.5 Summary

Stem cells are inherently capable of self-replication and expansion, engraftment, long-term survival in a host environment, and extensive migration. In various circumstances, they can be used to supply missing proteins, provide neuroprotection and trophic support to host cells, or even reconstruct missing or damaged neural architecture.

Significant challenges to successful human therapy with SCs remain, including overcoming barriers to CNS administration, modulating the host environment and immune response, and accomplishing *in vivo* the tracking of transplanted SCs. Recent scientific developments hold promise for mitigating ethical concerns about and practical limitations on sources of SCs for human therapy.

Pearls

- A variety of SCs are available for potential use in human therapy, including totipotent embryonic cells and pluripotent, or lineage-specific, “adult” SCs.
- SCs for CNS therapy may be delivered with transvascular, intrathecal, or direct surgical transplantation strategies, or a combination of these, depending on disease state, cell line, and transplantation goals.
- Mitigation of negative host factors, immunosuppression, and in vivo cellular tracking represent ongoing challenges in human SC therapy.
- Significant ethical and regulatory challenges to SC therapy deserve the careful attention of all clinicians involved in investigational SC therapy.

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8 Neurogenetic Basis of Pediatric Neurosurgical Conditions

Claudia C. Faria, Yuzo Terakawa, and James T. Rutka

In the past decade, significant progress has been made in increasing our understanding of the molecular genetic basis of neurosurgical disorders. As an example, an integrative genomics approach to a large cohort of medulloblastomas has shown that these tumors comprise four separate molecular subgroups with distinct demographics, clinical presentations, transcriptional profiles, genetic abnormalities, and clinical outcomes.¹ Furthermore, a genome-wide association study has recently identified the first susceptibility gene for moyamoya disease.² Although the molecular basis of pediatric neurosurgical diseases has not been fully elucidated, the application of advanced techniques in molecular biology to the research of neurosurgical diseases is contributing to our understanding of the molecular basis underlying pediatric neurosurgical conditions. In this chapter, we summarize the genetic basis of neurosurgical conditions like neoplasms, cerebrovascular diseases, and congenital and developmental disorders, especially focusing on common pediatric neurosurgical diseases.

8.1 Neurogenetic Basis of Common Pediatric Neurosurgical Diseases

8.1.1 Neoplasms

Diffuse Astrocytoma

Pediatric astrocytomas are histologically similar to adult astrocytomas; however, the extent to which the molecular pathogenesis of adult astrocytomas is similar to that of pediatric astrocytomas is unclear. Indeed, previous cytogenetic studies of high-grade pediatric astrocytomas in which comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) was used have demonstrated distinct patterns of copy number alterations from adult astrocytomas³ and infrequent copy number alterations in pediatric astrocytomas as opposed to those frequently seen in adult astrocytomas.^{4,5} More recently, advanced microarray-based genetic approaches have also been used to investigate pediatric astrocytomas. Genome-wide profiling with single-nucleotide polymorphism (SNP) arrays performed in 18 pediatric and 6 adult cases of glioblastoma multiforme (GBM) suggested that pediatric and adult GBMs are two molecularly distinct diseases, even though they have a few copy number alterations in common.⁶ Similarly, SNP arrays that interrogated copy number alterations in 78 pediatric high-grade gliomas have revealed significant differences in copy number alterations between pediatric and adult GBMs,⁷ suggesting that pediatric astrocytomas show distinct biological behavior and most likely have a different molecular pathogenesis.

Although amplification of the epidermal growth factor receptor (*EGFR*) gene is seen in up to 40% of adult glioblastomas and 15% of adult anaplastic astrocytomas, it is not commonly seen in pediatric astrocytomas.⁸ Nevertheless, high expression levels of *EGFR* were found by immunohistochemistry in 80% of pediatric non-brainstem high-grade gliomas. Mutations of the

PTEN gene at the 10q23 locus are rare in pediatric high-grade astrocytomas,⁹ but significant correlations between the presence of *PTEN* mutation and decreased survival have been demonstrated in high-grade pediatric astrocytomas. Moreover, frequent heterozygous deletions of 10q23 have been shown by FISH in 61% of 44 pediatric GBMs, and those cases harboring 10q23 deletions were associated with a significantly shorter overall survival time.¹⁰ Mutations of *p53* in pediatric high-grade astrocytomas have been reported in fewer than approximately 40% of cases.⁹ Overexpression of *p53* as determined by immunohistochemistry is strongly associated with an adverse outcome in pediatric gliomas.¹¹ In one series of 29 high-grade pediatric astrocytomas, inactivation of the *p53/MDM2/p14ARF* pathway by mutation of *p53*, overexpression of *MDM2*, or deletion of *p14ARF* was seen in over 95% of the cases, whereas the *pRb/cyclin D1/CDK4/p16* pathway was inactivated only in up to 25%, as opposed to over 80% of the corresponding adult tumors.⁸

Diffuse intrinsic pontine glioma (DIPG) is another entity of diffuse astrocytomas most often seen in the pediatric population; however, relatively little is known about the molecular genetics underlying DIPGs, probably because of a lack of availability of primary surgical specimens. A previous study has found a particularly high rate of *p53* mutations (71%) in seven pediatric DIPG cases. Another study has demonstrated *EGFR* overexpression and/or *EGFR* amplifications in 14 of 16 high-grade DIPGs, whereas only two of 12 low-grade DIPGs exhibited a low level of *EGFR* expression.¹² More recently, the role of two other genes—namely, *PDGFRA* and poly (ADP-ribose) polymerase-1 (*PARP1*)—has been implicated in DIPGs with the use of comprehensive SNP microarrays.^{7,13}

Pilocytic Astrocytoma

Early cytogenetic studies by CGH failed to demonstrate common cytogenetic aberrations in pilocytic astrocytomas, revealing few abnormalities in general. Among the few aberrations, gain of chromosome 7 was one of the most common events seen in pediatric pilocytic astrocytomas. Cytogenetic abnormalities were seen more commonly in patients older than 15 years than in patients younger than 15 years,¹⁴ and adult cases had much more complex karyotypes, with multiple areas of gains and losses. One of the most important studies in pilocytic astrocytomas during the past decade was an array-based CGH study that identified gains of the *BRAF* locus at the 7q34 locus.¹⁵ In this study, a tandem duplication of the *BRAF* locus was seen in 28 cases and p.V600E activating point mutations of *BRAF* in three cases of 53 pilocytic astrocytomas, demonstrating the potentially important role of *BRAF* and subsequent activation of the mitogen-activated protein kinase (MAPK) signaling pathway in pilocytic astrocytoma pathogenesis. Further molecular mechanisms with regard to the *BRAF* gene and MAPK pathway activation have recently been described.^{16–18} The incidence of *p53* mutations in pilocytic astrocytomas is controversial, with some authors reporting only infrequent *p53* mutations, whereas other authors report more frequent mutations. Mutations

of *PTEN* have rarely been reported in pilocytic astrocytomas. Protein expression of *p16*, *CDK4*, and *PTEN* was detected in 73%, 61%, and 38% of pilocytic astrocytomas, respectively.¹⁹

Medulloblastoma

Medulloblastoma has been reported in the setting of several different hereditary cancer syndromes, including Li-Fraumeni syndrome, Gorlin syndrome, Turcot syndrome, and Rubinstein-Taybi syndrome.²⁰ The Li-Fraumeni syndrome is associated with germline mutations in the *p53* gene. Patients with Li-Fraumeni syndrome have an increased risk for the development of embryonal tumors (including medulloblastoma) and choroid plexus carcinoma, among many other cancers. Patients with Gorlin syndrome (nevroid basal cell carcinoma syndrome) have germline mutations in the *PTCH1* gene, a component of the sonic hedgehog (SHH) signaling pathway, and up to a 5% risk for developing medulloblastoma. Germline mutations in the *SUFU* gene, a downstream mediator of the SHH pathway, have also been shown in patients with medulloblastoma.²¹ Germline mutations of the *APC* gene, a component of the Wnt signaling pathway, are seen in patients with Turcot syndrome, who have an increased risk for colorectal carcinoma and brain tumors, predominantly medulloblastoma. Children with Rubinstein-Taybi syndrome have a complex developmental disorder that includes broad thumbs and toes, characteristic facies, severe developmental delay, and a predisposition to malignancy, including medulloblastoma, oligodendroglioma, and meningioma. This syndrome is secondary to deletion/mutation of the Creb binding protein gene (*CBP*), which functions in three pathways involved in medulloblastoma pathogenesis (SHH, Wnt, and *p53*).²²

The most common cytogenetic changes observed in medulloblastoma are loss of chromosome 17p, often through the formation of an isochromosome 17q (loss of one copy of the short arm and gain of one copy of the long arm) and gain of chromosome 7. Other chromosomes frequently found to be lost are 6, 8p, 9q, 10q, 11 and 16q. Genes frequently amplified and/or overexpressed include *MYC*, *ERBB2*, *OTX2*, *PDGFRA*, and *CDK6*.²³

Recently, large genomic analyses have shed some light into the genetic landscape of medulloblastoma and allowed its stratification into molecular subgroups (► Fig. 8.1). Four independent studies used integrated genomics and established the existence of a Wnt subgroup, an SHH subgroup, and multiple non-Wnt/SHH subgroups. A recent working committee renamed these last subgroups as group 3 and group 4 medulloblastomas, which are currently still poorly understood.²⁴ The Wnt subgroup has a very good prognosis, with long-term survival rates exceeding 90%. The most common genetic alterations found are *CTNNB1* mutations and monosomy 6. SHH medulloblastomas have changes in components of the SHH pathway, such as somatic mutations of *PTCH*, *SMO*, and *SUFU* and amplifications of *GLI1* and *GLI2*. This subgroup is more common in young children and in adults, who have an intermediate prognosis between that of the Wnt subgroup (very good) and that of group 3 (poor). Group 3 is characterized by frequent amplifications of *MYC* and by changes in genes involved in the photoreceptor or GABAergic (γ -aminobutyric acid) signaling. Patients in this group have a high incidence of metastasis and a dismal prognosis. The most common cytogenetic alterations seen in group 4 medulloblastomas are isochromosome 17q (66%) and loss of

	Age	Genetic Profile	5-Year Overall Survival
Wnt	Unimodal Range: 3-17 y (median=9.5)	Wnt signaling <i>CTNNB1</i> mutation Monosomy 6 <i>MYC</i> +	94% Rare M+
SHH	Bimodal ≤ 3 y; ≥ 16 y	SHH signaling <i>PTCH1/SMO/SUFU</i> mutation <i>GLI2</i> and <i>MYCN</i> amplification <i>MYCN</i> +	87% Uncommon M+
Group 3	Unimodal Range: 1-10 y (median=5)	Photoreceptor/GABAergic signaling <i>MYC</i> amplification <i>MYC</i> +++	32% Very frequent M+
Group 4	Unimodal Range: 2-36 y (median=9)	Neuronal/ glutamatergic <i>i17q; CDK6</i> and <i>MYCN</i> amplification Minimal <i>MYC/MYCN</i>	76% Frequent M+

Fig. 8.1 Molecular subgroups of medulloblastoma, including age distribution, genetic profile, survival rate, and incidence of metastasis. GABA, γ -aminobutyric acid.

the X chromosome (80% of female patients). Genes involved in the neuronal or glutamatergic pathways have also been identified, although their genetic or clinical relevance is yet to be clarified.²⁴

Ependymoma

There are few known familial ependymoma syndromes. Spinal intramedullary ependymomas are frequently diagnosed in individuals with neurofibromatosis type 2 (NF2) and are one classic manifestation of the disease. Ependymomas have also been reported in patients with Turcot syndrome (colonic neoplasia and central nervous system neoplasia). These individuals have germline mutations in the *APC* gene on chromosome 5. Ependymomas have been reported in individuals with multiple endocrine neoplasia type I (MEN1) secondary to mutation of a tumor suppressor gene on chromosome 11q13. Rare families where multiple individuals have ependymomas in the absence of other known germline mutation syndromes have been described.

Over the years, numerous chromosomal abnormalities were reported in ependymoma by studies using karyotyping and CGH. Common genetic anomalies include loss of chromosome 1p, 3, 6q, 9p, 10q, 13q, 16p, 17, 21, and 22q as well as gains of 1q, 4q, 5, 7, 8, 9, 12q, and 20.²⁵ The most common losses seen in children were loss of chromosome 6q, followed by 22q. The regions most frequently amplified in pediatric ependymoma are chromosomes 1q and 9. Gains of 1q are associated with posterior fossa ependymomas, anaplastic features and unfavorable outcome.²⁶

With advances in microarray technology, copy number variations could be mapped at much higher resolutions. Using array

CGH, Taylor *et al.* profiled 103 ependymomas and found three molecularly distinct subgroups, correlated with the anatomical location of the tumor in the supratentorial, posterior fossa, or spinal compartments.²⁷

Similar to array CGH, gene expression profiling studies were able to distinguish tumor-specific signatures according to anatomical location.^{27,28} Supratentorial ependymomas had high expression levels of *EPHB-EPHRIN* (*EPHB2/3/4* and *EPHRINA3/4*), *NOTCH* (*JAGGED1/2*), and genes involved in cell cycle regulation (*CYCLINB2/D1/G2*, *CDK2/4*, and *CDKN1C/2C*). Posterior fossa tumors highly expressed genes inhibitors of differentiation (*ID1/2/4*) and members of the aquaporin family (*AQP1/3/4*). Finally, spinal ependymomas showed up-regulation of various homeobox genes (*HOXA7/9*, *HOXB6/7* and *HOXC6/10*) and insulin-like growth factor 1 (*IGF1*). More recently, Witt *et al.* transcriptionally profiled two large independent cohorts of posterior fossa ependymomas and identified two clinically and molecularly distinct subgroups.²⁹ Group A patients were younger, with tumors located laterally in the cerebellum, and with a balanced genome. This subgroup was also associated with worse clinical outcome and higher incidence of metastasis and recurrence (► Fig. 8.2). In contrast, Group B patients had tumors in the midline and a better prognosis. The candidate marker genes to distinguish the two groups were upregulation of *LAMA2* in Group A and *NELL2* in Group B.²⁹

Other genetic abnormalities were described in ependymomas, including focal amplifications of *MYCN*, *EGFR* and *YAP1* and deletion of *CDKN2A* and *SULT4A1*. The interesting finding from these studies is that up to 40% of pediatric ependymomas appear to have a balanced genomic profile raising the possibility that epigenetic mechanisms may play an important role in ependymoma pathogenesis.

Atypical Teratoid/Rhabdoid Tumors

Atypical teratoid/rhabdoid tumors (AT/RTs) are aggressive embryonic tumors that are usually diagnosed in children younger than 2 years (► Fig. 8.3). They are frequently misdiagnosed as medulloblastoma/primitive neuroectodermal tumor

(PNET), especially on small biopsies, as up to 70% of rhabdoid tumors contain fields of cells indistinguishable from PNET. As well as occurring in the central nervous system (CNS), rhabdoid tumors are also seen in the kidneys and less commonly in a variety of locations in the soft tissues. Versteeg and colleagues identified the tumor suppressor gene on chromosome 22q11 as the *SMARCB1* gene, also called *hSNF5/INI1*.³⁰ The *SMARCB1* gene was biallelically inactivated by deletions and/or truncating mutations in a series of renal rhabdoid tumors and cell lines, suggesting that it acts as a classic tumor suppressor gene. This was confirmed by the reintroduction of the gene to cell lines from

	Group A	Group B
Patient's age	Median 2.5 y	Median 20 y
Tumor location	67% laterally	95% in the midline
Genetic profile	Balanced genomic profile	Loss of chromosomes 1, 2, 3, 6, 8, 10, 14q, 17q, and 22q; gain of 4, 5q, 7, 9, 11, 12, 15q, 18, 20, and 21q
Antigen markers	LAMA2	NELL2
5-Year recurrence	56% (higher incidence of metastasis)	25%
5-Year overall survival	69%	95%

Fig. 8.2 Molecular subgroups of ependymoma, including clinical and molecular profiles.

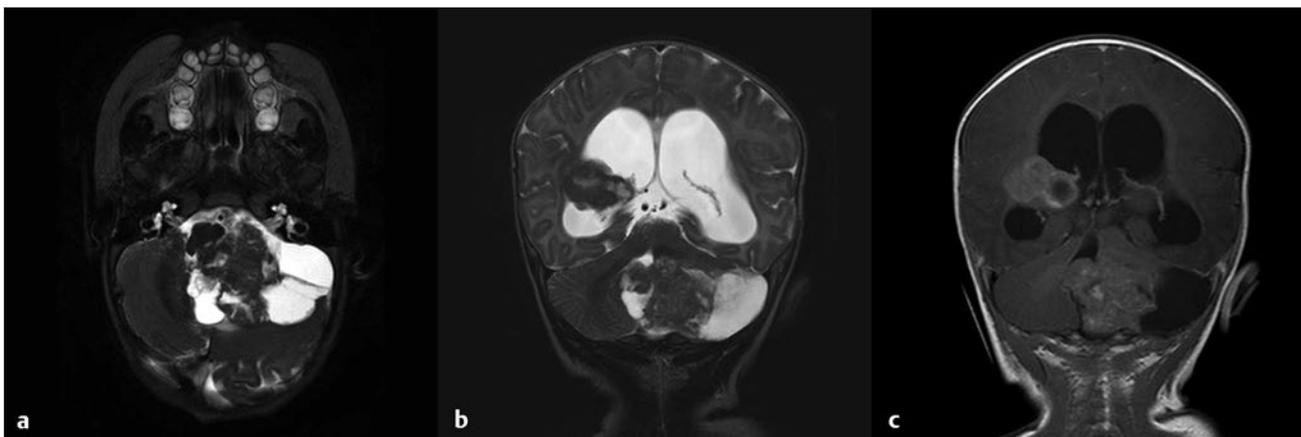


Fig. 8.3 Magnetic resonance images of an atypical teratoid/rhabdoid tumor of the posterior fossa and right lateral ventricle. (a) T2-weighted axial image demonstrating a large mass with cystic component in the posterior fossa and mass effect on the brainstem. (b) T2-weighted and (c) T1-weighted coronal images with gadolinium demonstrating both the posterior fossa and the right lateral ventricle lesions, with obstructive hydrocephalus.

AT/RTs deficient in *SMARCB1*, which resulted in dramatic cessation of growth, cell cycle arrest, apoptosis, and expression of markers of cell senescence.³¹

Biegel and co-investigators went on to show somatic deletions and/or truncating mutations of *SMARCB1* in CNS rhabdoid tumors.³² It was shown that some children with rhabdoid tumors have de novo germline mutations of *SMARCB1*, suggesting that these children were born with “one hit” in the *SMARCB1* gene and were predisposed to develop rhabdoid tumors.³² In some rare families with an elevated incidence of rhabdoid tumors and/or choroid plexus carcinomas, there may be an inherited germline mutation of the *SMARCB1* gene that predisposes affected family members to cancer.²⁰ At least 80% of AT/RTs have genomic mutations of the *SMARCB1* gene. Of the remaining 20%, many have decreased expression of *SMARCB1* at the protein or RNA level.

The *SMARCB1* protein is a member of the SWI/SNF adenosine triphosphate (ATP)-dependent chromatin remodeling complex. It functions to regulate the structure of DNA (chromatin) to either allow or deny access of transcription factors to their respective promoters. The SWI/SNF complex contains about 10 components, raising the possibility that genetic alterations of members other than *SMARCB1* could be involved in AT/RT pathogenesis. Recently, inactivation of the ATPase subunit *SMARCA4* (also known as *BRG1*) was shown in the tumor cells of two sisters with rhabdoid tumors lacking the *SMARCB1* mutation.³³ Another case of a supratentorial AT/RT in a child was reported to have a homozygous *SMARCA4* mutation with retained *SMARCB1* staining.³⁴

8.1.2 Cerebrovascular Diseases

Cerebral Cavernous Malformation

Cerebral cavernous malformations (CMs), also known as cavernomas, cavernous angiomas, or cavernous hemangiomas, are congenital vascular hamartomas that consist of thin-walled vascular channels without intervening normal brain parenchyma. Although cerebral CMs can occur sporadically, some may arise in an autosomal-dominant inherited form (► Fig. 8.4). Genetic linkage analyses in cerebral CMs have mapped and identified cerebral CM genes at three different loci: *CCM1* on human chromosome 7q21.2, *CCM2* on 7p15-p13, and *CCM3* on 3q25.2-q27.³⁵ These cerebral CM genes encode proteins called K-Rev interaction trapped 1 (Krit1), *MGC4607*, and Programmed Cell Death 10 (PDCD), respectively. The cerebral CM proteins interact with each other and regulate endothelial cell-to-cell adhesion, cell shape remodeling, and cell adhesion to the extracellular matrix, as reviewed recently.³⁶ To date, a number of germline mutations on these genes have been reported, and almost all mutations lead to a premature termination codon, resulting in a loss of protein function. Although the precise mechanism of inherited cerebral CM pathogenesis has not yet been clarified, a two-hit mechanism is implicated in cerebral CM formation,³⁷ as was suggested by Knudson⁵⁸ in retinoblastoma formation (► Fig. 8.5). According to this two-hit model, cerebral CM formation requires a complete loss of any of the three cerebral CM proteins within endothelial cells lining capillary cavities, which results from a germline mutation in one of the two alleles (first hit) and a somatic mutation in the other allele

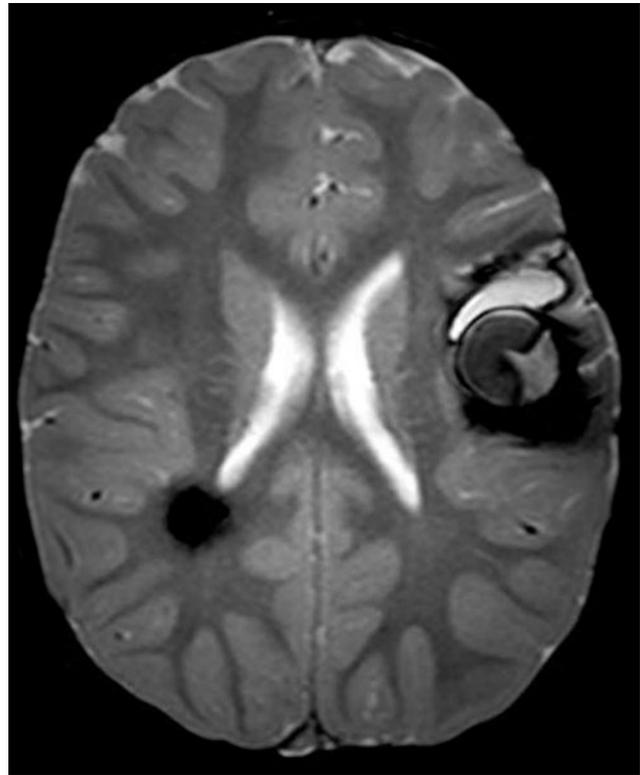


Fig. 8.4 Axial multiplanar gradient-recalled magnetic resonance image showing hemosiderin alterations in the left insular area and right posterior periventricular region. These lesions represent cavernous malformations, and the presence of multiple lesions suggests the diagnosis of familial cerebral cavernous malformation.

(second hit). In fact, biallelic germline and somatic mutations in each of the three cerebral CM genes have recently been reported, strongly supporting the two-hit mechanism of cerebral CM formation.^{38–40}

Moyamoya Disease

Moyamoya disease is a progressive cerebral angiopathy characterized by bilateral stenosis or occlusion of the terminal portion of the internal carotid arteries and/or proximal portions of the anterior and the middle cerebral arteries, accompanied by an aberrant collateral vascular network called moyamoya vessels (► Fig. 8.6). Moyamoya disease is known to be most prevalent in East Asian countries, such as Japan, Korea, and China,⁴¹ and has a higher prevalence in females, with a female-to-male ratio ranging from 1.8:1 to 2.18:1.^{41,42} Given the fact that in Japan approximately 12 to 15% of moyamoya diseases are familial forms,⁴¹ genetic factors have been implicated in the pathogenesis of moyamoya disease. Previous linkage analyses have revealed several gene loci at 3p24.2-p26, 6q25, 8q23, and 17q25.3 linked to moyamoya disease⁴³; however, relevant genes predisposing to this disease have remained largely unknown until recently. One of the most promising discoveries in this disease was shown in a recent genome-wide association study, which first identified a susceptibility gene for moyamoya disease called *RNF213* at the 17q25.3 locus.² A more extensive study characterized the biological role of the RNF213 protein in

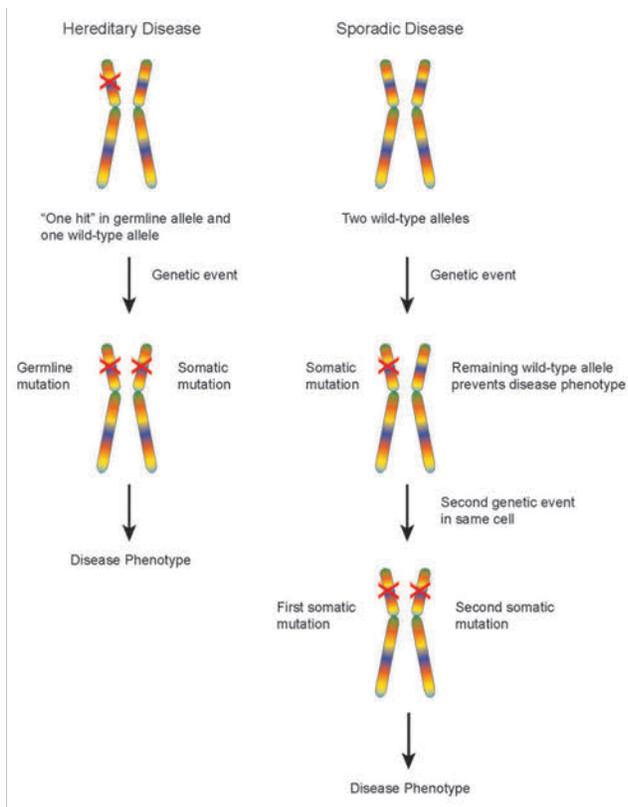


Fig. 8.5 Knudsonian two-hit mechanism was originally described in families in which multiple individuals were affected with retinoblastoma. Children in these families developed tumor(s) at a younger age and were more likely to develop multiple tumors. Knudson suggested that these children were born with one “hit” in the germline, so only one additional somatic event was required for tumorigenesis to occur. Children with sporadic tumors were born with no hits in the germline, and therefore two hits were required in any given cell for a tumor to be initiated. This would account for the lower incidence of tumors in the general population, the later age at onset, and absence of multiple tumors. This two-hit mechanism theory has been implicated in other neurosurgical diseases, such as familial cerebral cavernous malformation.

angiogenesis in zebrafish.⁴³ A further genetic study of *RNF213* in Japanese patients with moyamoya disease has demonstrated an *RNF213* sequence variant, c.14575G > A, resulting in an arginine to lysine substitution, in 39 of 41 familial cases of moyamoya disease (95.1%), in 129 of 163 sporadic cases (79.2%), and in 5 of 283 normal control individuals (1.8%). Interestingly, a homozygous c.14576G > A variant significantly correlated with earlier onset of the disease and known poor prognostic factors, such as infarctions at initial manifestation and involvement of the posterior cerebral arteries, suggesting that it may be used as a predictive factor for severe moyamoya disease.⁴⁴ Future studies will undoubtedly clarify the role of the *RNF213* gene in moyamoya disease.

8.1.3 Congenital and Developmental Disorders

Craniosynostosis

Craniosynostosis, characterized by premature fusion of one or more skull sutures, is one of the most common craniofacial anomalies, with an estimated incidence of approximately 1 in 2,500 live births.⁴⁵ Since a specific missense mutation in the *MSX2* gene was first described in association with craniosynostosis in 1993, several causative genes have been identified associated with the pathogenesis of craniosynostosis. To date, mutations in the *TWIST1*, *EFNB1*, *POR*, and *RAB23* genes and in three of the four fibroblast growth factor receptor (FGFR) family of genes, *FGFR1*, *FGFR2*, and *FGFR3*, have been shown to be involved with several types of craniosynostosis (► Table 8.1). A recent genetic and cytogenetic study in a large cohort of patients with craniosynostosis has found genetic causes of craniosynostosis in 21% of the cases, consisting of chromosome abnormalities in 14% and single-gene mutations in 86%. Among those cases with genetic alterations in this series, mutations were seen most frequently in *FGFR2* (32%), followed by *FGFR3* (25%), *TWIST1* (19%), and *EFNB1* (7%).⁴⁶

The *FGFR* genes encode transmembrane tyrosine kinase receptors, which consist of an extracellular ligand-binding domain with three immunoglobulin-like loops (IgI, IgII, and IgIII),

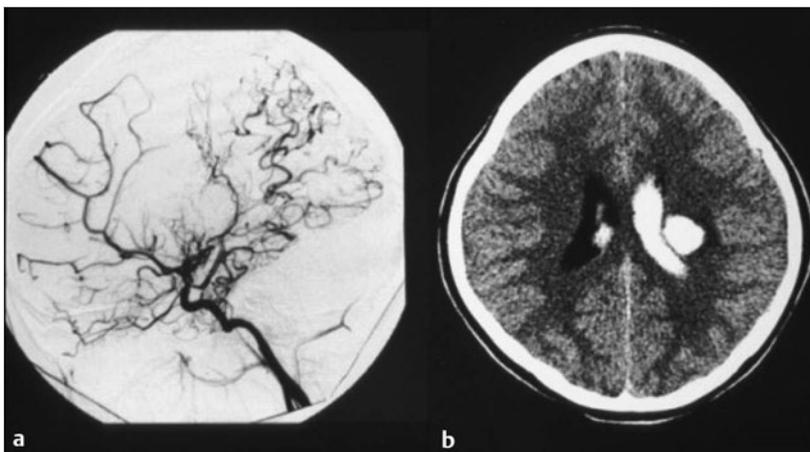


Fig. 8.6 Moyamoya disease. (a) Lateral cerebral angiogram showing stenosis of the posterior circulation with recruitment of extracranial arterial supply to the parietal and occipital lobes. (b) In same patient, computed tomography scan showing left parenchymal and intraventricular hemorrhage as a result of moyamoya disease.

Table 8.1 Known associations of craniosynostosis and gene mutations

Phenotype	Mutated gene	Chromosomal location
Pfeiffer syndrome	<i>FGFR1</i> (<5%) <i>FGFR2</i> (>95%)	8p11 10q26
Apert syndrome	<i>FGFR2</i>	10q26
Crouzon syndrome	<i>FGFR2</i>	10q26
Crouzon syndrome with acanthosis nigricans	<i>FGFR3</i>	4p16
Jackson-Weiss syndrome	<i>FGFR2</i>	10q26
Beare-Stevenson syndrome	<i>FGFR2</i>	10q26
Muenke syndrome	<i>FGFR3</i>	4p16
Saethre-Chotzen syndrome	<i>TWIST1</i>	7p21
Craniofrontonasal syndrome	<i>EFNB1</i>	Xq12q13.1
Boston-type craniosynostosis	<i>MSX2</i>	5q35
Antley-Bixler syndrome	<i>POR</i>	7q11
Carpenter syndrome	<i>RAB23</i>	6p11

a transmembrane domain (TM), and two split intracellular tyrosine kinase domains (TK1 and TK2). Binding of its ligand, fibroblast growth factor, to FGFRs induces FGFR dimerization and autophosphorylation, subsequently leading to phosphorylation of downstream signaling elements. Mutations in *FGFR2*, the most common genetic event in craniosynostosis, are largely localized, but not limited, to the linker region between IgII and IgIII or in the IgIII loop encoded by exon IIIa or IIIc,^{47,48} and these mutations result in constitutive activation of the receptor or increased affinity for ligand. In contrast, most mutations seen in *TWIST1*, which encodes a transcription factor with a basic helix–loop–helix domain, are likely to produce premature termination of the protein, resulting in a loss of protein function. Further details underlying the molecular mechanisms of craniosynostosis are well described in the literature.⁴⁸

Holoprosencephaly

Holoprosencephaly is the most common developmental defect of the forebrain and midface and results from incomplete midline cleavage of the prosencephalon. Neurosurgeons are frequently involved in these cases when hydrocephalus develops and requires cerebrospinal fluid diversion. Holoprosencephaly is genetically and phenotypically heterogeneous, and the “multiple-hit” hypothesis is now a widely accepted model for this disease.⁴⁹ According to this model, combinations of mutations in different genes lead to holoprosencephaly with various degrees of severity.⁵⁰ Point mutations or deletions in four major genes are the leading cause of holoprosencephaly susceptibility: *SHH* (7q36), *ZIC2* (13q32), *SIX3* (2p21), and *TGIF* (18p11.3).⁵¹ Additional genes with a less important role in the occurrence of holoprosencephaly have also been identified: *GLI2* (2q14), *PTCH1* (9q22.3), *DISP1* (1q42), *NODAL* (10q22.1), and *FOXH1* (8q24.3). These minor genes are infrequently mutated or deleted, and the dysfunction of only one of them appears insufficient to cause severe disease phenotypes.⁵¹

Recently, a large study including 645 probands and their relatives found mutations in the four main genes in 25% of cases.⁴⁹ Mutations in the *SHH*, *SIX3*, and *TGIF* genes were inherited in more than 70% of cases, while 70% of *ZIC2* mutations occurred de novo. The authors also showed a positive correlation between the severity of the holoprosencephaly phenotype and mutations in the *SHH*, *SIX3*, and *TGIF* genes, but no correlation was found with *ZIC2* mutations. Fifteen cases of double mutation were reported, which supports the hypothesis of holoprosencephaly as a multiple-hit process.⁴⁹

Lissencephaly

Lissencephaly is a neuronal migration disorder characterized by a lack of the normal cortical convolutions that produce cortical thickening and a smooth cerebral surface.

There are two pathologic subtypes: classic or type 1 lissencephaly and cobblestone or type 2 lissencephaly.

To date, type 1 lissencephaly has been associated with mutations of six genes, *LIS1*, *DCX*, *TUBA1A*, *ARX*, *RELN*, and *VLDLR*.⁵² Mutations in these genes are associated with different disease phenotypes that include isolated lissencephaly (without any associated malformation outside the brain), Miller–Dieker syndrome, subcortical band heterotopia, X-linked lissencephaly with abnormal genitalia, and lissencephaly with cerebellar hypoplasia (► Table 8.2). The *LIS1* gene on chromosome 17p13.3 controls mitotic spindle orientation, and its deletion causes dysfunction of dynein, a microtubular protein involved in neuronal migration. Complete deletion of both *LIS1* and the *YHAWAE* gene on chromosome 17p13 causes the Miller–Dieker syndrome, a severe form of type 1 lissencephaly associated with facial dysmorphisms. The *DCX* gene on chromosome Xq22.3 encodes a microtubule-associated protein, and its mutation causes classic lissencephaly in males and a migration disorder called subcortical band heterotopia in females.⁵³ Recently, *TUBA1A* (alpha tubulin complex) mutations on chromosome 12q12–q14 were also described in classic lissencephaly. This gene encodes alpha tubulin protein, a major component in microtubule assembly that is essential for neuronal migration. The *ARX* gene, located at Xp22.1, encodes a transcription factor expressed in interneurons of the forebrain and in the male gonad. *ARX* mutations cause X-linked lissencephaly with anomalous genitalia in affected hemizygous male children. The *RELN* gene on chromosome 7q22.1 encodes an extracellular matrix-associated protein (reelin) that plays a critical role in regulating neuronal migration during cortical development. This protein interacts with the very low-density lipoprotein receptor (*VLDLR*), activating downstream signaling that influences cell migration. Patients with mutations in these genes have lissencephaly associated with cerebellar hypoplasia and the absence of foliation.⁵⁴ Several genes have been implicated in the etiology of type 2 lissencephaly, and three syndromes were described: Walker–Warburg syndrome, Fukuyama congenital muscular dystrophy, and muscle–eye–brain disease (see ► Table 8.2). All these genes are involved in the glycosylation of components of extracellular matrix. When mutations occur, the integrity of the superficial cortical layer is compromised, and neurons overmigrate into the pial surface, giving origin to the typical cobblestone appearance.⁵²

Gene	Locus	Associated phenotype
Type 1 lissencephaly (classic)		
<i>LIS1</i>	17p13.13	Isolated lissencephaly
<i>LIS1 + YHAWAE</i>	17p13.13	Miller-Dieker syndrome
<i>DCX</i>	Xq22.3-q23	X-linked lissencephaly (males) Subcortical band heterotopia (females)
<i>TUBA1A</i>	12q13.12	Isolated lissencephaly
<i>ARX</i>	Xp22.1	Isolated lissencephaly with abnormal genitalia
<i>RELN</i>	7q22.1	Lissencephaly with cerebellar hypoplasia
<i>VLDLR</i>	9p24.2	Lissencephaly with cerebellar hypoplasia
Type 2 lissencephaly (cobblestone)		
<i>POMT1</i>	9q34.13	Walker-Warburg syndrome Muscle–eye–brain disease
<i>POMT2</i>	14q24.3	Walker-Warburg syndrome Muscle–eye–brain disease
<i>FKRP</i>	19q13.32	Walker-Warburg syndrome Muscle–eye–brain disease
<i>FCMD</i>	9q31.2	Fukuyama congenital muscular dystrophy Walker-Warburg syndrome
<i>LARGE</i>	22q12.3	Muscle–eye–brain disease
<i>POMGnT1</i>	1p34.1	Muscle–eye–brain disease

Congenital Hydrocephalus

Congenital hydrocephalus is a critical neurosurgical disorder that comprises diverse conditions. These include primary hydrocephalus and secondary forms of hydrocephalus caused by antecedent events like intrauterine infections, trauma, intracranial hemorrhages, and tumors. Congenital hydrocephalus can also occur in association with neural tube defect or other CNS malformations (► Fig. 8.7).⁵⁵ Primary congenital hydrocephalus is not a rare disease, with an estimated incidence of approximately 0.2 to 0.8 per 1,000 live births.⁵⁶ However, genetic causes of this condition are not yet fully understood. A recent retrospective survey of a total of 75 patients with primary congenital hydrocephalus found cytogenetic or genetic abnormalities, such as trisomy 9 and L1 syndrome, in 14 of the 75 cases, but the cause of hydrocephalus was not detected in the rest of the cases.⁵⁵

L1 syndrome, an X-linked recessive disorder, is known to be the most common genetic cause of congenital hydrocephalus so far,⁵⁵ accounting for approximately 5% of cases of congenital hydrocephalus in males. It is characterized by hydrocephalus, agenesis or hypoplasia of the corpus callosum and corticospinal tracts, lower limb spasticity, mental retardation, and adducted thumbs, and it comprises several overlapping clinical phenotypes: X-linked hydrocephalus; MASA syndrome (*mental*

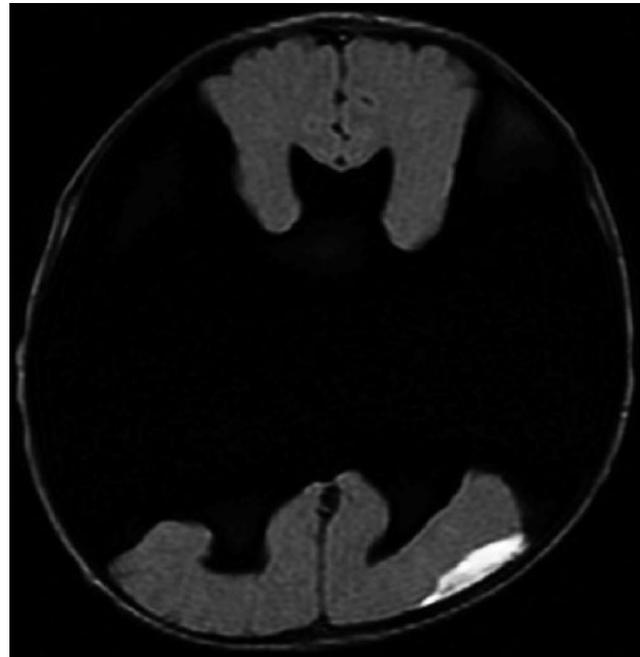


Fig. 8.7 Axial T1-weighted magnetic resonance image of a newborn with hydrocephalus caused by bilateral, severe schizencephaly. Schizencephaly is a neuronal migration disorder similar to holoprosencephaly and other congenital central nervous system malformations, but the genetics of this entity have yet to be elucidated completely.

retardation, aphasia, shuffling, and adducted thumbs); X-linked hereditary spastic paraplegia type 1; and X-linked agenesis of the corpus callosum (► Fig. 8.8). The *L1CAM* gene at Xq28, which encodes L1 protein (neural cell adhesion molecule), is responsible for L1 syndrome. Since the first report of aberration in the *L1CAM* gene in an affected family with X-linked hydrocephalus, a number of *L1CAM* mutations have been described in association with L1 syndrome.⁵⁷ Furthermore, previous studies have provided close correlations between severity of L1 syndrome and mutation types in L1 protein.⁵⁷ For example, mutations leading to extracellular L1 protein truncation or absence tended to produce more severe clinical manifestations than mutations in the cytoplasmic L1 protein domain. Thus, *L1CAM* mutation analysis in L1 syndrome is becoming a clinically useful tool, not only for precise genetic counseling and prenatal diagnosis within affected families but also for prognosis.

8.2 Conclusion

The revolution in molecular genomics has allowed a better characterization of the genetic origins of pediatric neurosurgical diseases. The identification of molecular and clinical subtypes, along with the selection of reliable and validated biomarkers, adds another layer of relevance in patient care and opens avenues for future targeted therapies. Next-generation sequencing will also provide an enormous amount of data on the dysregulated signaling pathways and driver mutations, which will allow a better understanding of pathogenesis and the subsequent development of accurate preclinical models. The major challenge is to make these techniques a simple,

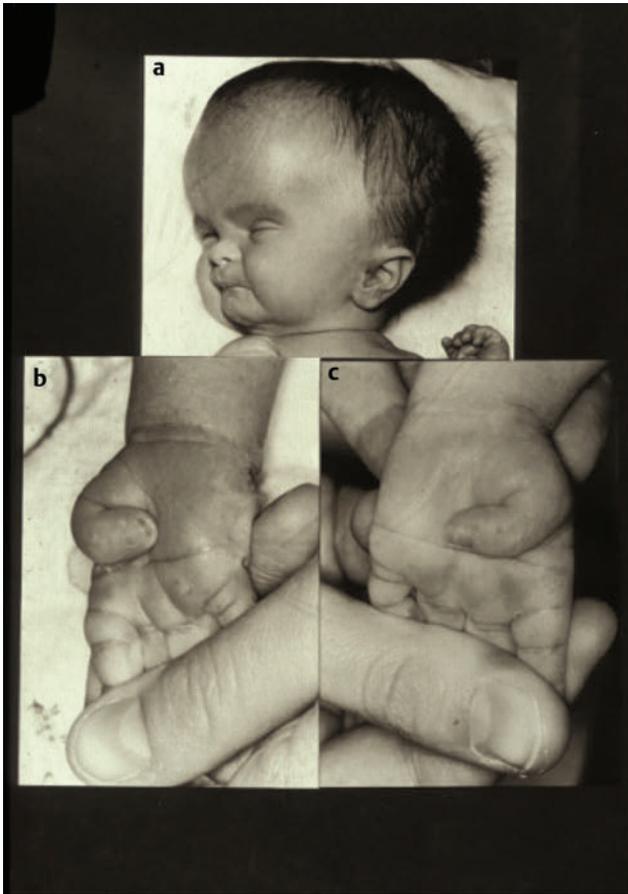


Fig. 8.8 X-linked hydrocephalus. (a) Newborn with macrocephaly and bulging anterior fontanel. (b,c) Typical flexor position of thumb in X-linked hydrocephalus.

available, and reproducible tool in clinical practice. The obvious impact will be more effective prognosis, a better assessment of response to therapy, and the discovery of novel therapies.

8.3 Acknowledgments

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Pearls

- A tandem duplication of the *BRAF* locus occurs in pilocytic astrocytoma.
- Molecular subclassification of medulloblastomas and ependymomas will allow the stratification of patients into appropriate risk groups and the tailoring of treatments according to the tumor genome.
- The first susceptibility gene for moyamoya disease, *RNF213*, has been identified.

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9 Hydrocephalus

Amal Abou-Hamden and James M. Drake

The surgical management of hydrocephalus has undergone fantastic changes over the last generation of neurosurgeons: dramatic improvements in imaging with computed tomography (CT) and magnetic resonance (MR) imaging, remarkable innovative advances in cerebrospinal fluid (CSF) valve technology, bewildering complex computer models, and dramatic advances in endoscopic equipment and techniques. In terms of overall patient outcomes, one could conclude, however, that things are a little better, but “not much.” This frustrating yet fascinating dichotomy between technological advances and clinical outcomes makes hydrocephalus, first described by the ancients, one of the most understated and complex disorders. For pediatric neurosurgeons, it is the disorder that they most commonly treat. The challenge to the current generation of pediatric neurosurgeons is to solve this vexing problem, through a better understanding of basic science, better computer models, further technological advances, and most importantly a broad-based, concerted multi-disciplinary attack on this disorder. This chapter focuses on an overview of pediatric hydrocephalus. Further chapters will address its management with CSF shunts and endoscopy.

9.1 Definition

Hydrocephalus is possibly most simply defined as an increase in the fluid-containing spaces of the brain at increased pressure, resulting from an imbalance between CSF production and absorption or flow. This definition excludes other abnormalities of CSF dynamics, such as benign intracranial hypertension, in which the ventricles are not enlarged, and hydrocephalus ex vacuo, in which cerebral atrophy and focal destructive lesions lead to an abnormal increase of CSF passively. However, not all cases fall clearly within these definitions; patients with parenchymal destruction may develop progressive hydrocephalus, and patients with slit-ventricle syndrome may have a presentation akin to that of benign intracranial hypertension.

9.2 Classification

There is no universally accepted classification system for hydrocephalus. A number have been suggested,¹⁻⁵ which include the following:

- Communicating versus noncommunicating
- Obstructive versus absorptive
- Acquired versus congenital
- Genetic or central nervous system (CNS) malformation-associated versus isolated
- Intraventricular-obstructive versus extraventricular
- Simple versus complicated

The terms *communicating* and *noncommunicating* date back to the early 1900s and are based on the experimental studies of Dandy and Blackfan,⁶ who investigated the pathophysiology of hydrocephalus in which the aqueduct is obstructed. *Communicating* implies that the CSF has free flow into the subarachnoid

space, but in the absence of overproduction, it is generally accepted that CSF absorption is impaired (or obstructed) downstream at some point. The terms *compensated hydrocephalus* and “*arrested*” *hydrocephalus* are also older and generally refer to whether an increase in ventricular size is associated with evidence of raised intracranial pressure (ICP). In some cases, the gradual increase in ventricular size stabilizes by reaching a new equilibrium, and the patient has no symptoms or signs of raised ICP. In others, a patient is discovered incidentally to have large ventricles unassociated with any identifiable problems. However, patients with apparently arrested hydrocephalus may still develop symptoms and signs at a later date, so the process is not entirely static.⁷ Congenital hydrocephalus is present at birth and often is associated with developmental defects; acquired hydrocephalus occurs after development of the brain and ventricles.^{4,8} Hydrocephalus has also been classified based on the stage of development at the time that the ventricles became dilated.⁹ The various subtypes of fetal hydrocephalus are classified according to the mechanism of obstruction to the flow of CSF; they include primary or simple hydrocephalus, with a single point of obstruction to flow; dysgenetic hydrocephalus, with complex abnormalities of the CNS, such as Arnold-Chiari malformation; and secondary hydrocephalus resulting from tumor or bleeding. This classification is cross-referenced to the stage of fetal development (i.e., neuronal maturation, cell migration). This classification may prove useful in deciding when treatment may be futile if the legal period for terminating a pregnancy has elapsed and in identifying potential candidates for early delivery or fetal surgery.⁵

Extraventricular obstructive hydrocephalus is now recognized to represent, almost universally, benign pericerebral collections of infancy that are usually familial, resolve with time, and almost never require treatment.¹⁰ Exceptions include genetic conditions, such as certain mucopolysaccharidoses, achondroplasia, Sotos syndrome, and glutaric aciduria type 1, which are often associated with developmental delay. In these cases, identification is important, as therapeutic options exist for many forms of mucopolysaccharidosis and for glutaric aciduria type 1.¹¹

9.3 Epidemiology

The exact incidence of hydrocephalus is hard to ascertain as it is generally secondary to some other insult, including tumor, infection, trauma, or prematurity. Cited rates in newborns range from 0.3 to 4 per 1,000 live births. When it occurs as a single congenital disorder, the incidence of hydrocephalus has been reported as 0.9 to 1.5 per 1,000 births.¹²⁻¹⁶ One estimate suggested that approximately 125,000 persons are living with CSF shunts and that 33,000 shunts are placed annually in the United States.¹⁷

The incidence of pediatric hydrocephalus has declined in many developed countries.¹⁰ Antenatal screening, genetic testing, and pregnancy termination have reduced the incidence of the congenital malformations of the brain that cause

hydrocephalus. The incidence of open neural tube defects has also decreased precipitously as a result of maternal folate supplementation, antenatal screening, and termination of pregnancy based on superior antenatal imaging with ultrasound and MR imaging. The incidence of CSF shunting in open neural tube defects, formerly reported to be as high as 90%, has also declined, possibly as a result of a generally more conservative approach, and the selection of anatomically lower lesions for delivery with a lower requirement for shunting.^{18,19} The incidence of intraventricular hemorrhage (IVH) has decreased as a result of better perinatal management of prematurity.²⁰

9.4 Cerebrospinal Fluid Production, Circulation, and Absorption

CSF is produced by two mechanisms. Most of the CSF (50 to 80%) is thought to be secreted by the choroid plexus within the cerebral ventricles. Extrachoroidal CSF production in subarachnoid sites and by way of a transependymal route has also been documented. About 20% or more of the CSF is derived from brain extracellular fluid created as a by-product of cerebral metabolism.^{21–23} Normally, rates of production (0.35 mL/min or approximately 400 to 500 mL/d) and absorption of CSF are equal. Total CSF volume is 65 to 140 mL in children and 90 to 150 mL in adults

The process of CSF formation by the choroid plexus includes plasma ultrafiltration and secretion. Secretion, an energy-dependent process, is initiated by hydrostatic pressure in the choroidal capillaries and by active transport of sodium. The enzymes sodium-potassium adenosine triphosphatase and carbonic anhydrase partly regulate CSF secretion.²³ CSF production has been reported to remain constant across the normal range of ICP,²⁴ with CSF production decreasing when the ICP approaches mean arterial pressure. There have been reports, however, of downregulation of CSF production in patients with chronic hydrocephalus.²⁵ In contrast to CSF production, CSF reabsorption is not an energy-dependent process.²² Information gained from MR imaging analysis of CSF movement demonstrates pulsatile to-and-fro motion of CSF within the lateral ventricles, produced from a brain-pumping motion that ejects the CSF and causes a net downward flow.²⁶

Historically, it has been held that CSF is absorbed into the vascular system mainly through the arachnoid villi within the arachnoid granulations covering the brain and spinal cord leptomeninges.^{27,28} This process is thought to be passive and not energy-dependent. A layer of endothelium within the arachnoid villi separates the subarachnoid CSF space from the vascular system. Water and electrolytes pass freely across these arachnoid membranes. There is normally a 5- to 7-mm Hg difference in pressure between the dural venous sinuses and the subarachnoid space. This is presumed to be the hydrostatic force behind the absorption of CSF. Larger proteins and macromolecules cannot pass through intercellular junctions but are selectively transported across the cytoplasm of endothelial cells by an active process involving micropinocytosis.²⁸ Increased absorption through the arachnoid villi protects the brain from transient increases in ICP.²⁹ This concept has, however, been

recently challenged. Newborn infants do not have visible arachnoid granulations yet maintain normal CSF circulation. Johnston et al^{30–32} have produced evidence in a number of animal species and human cadavers that the main route of CSF absorption is via the olfactory nerves, cribriform plate, and nasal lymphatics. At pressures above normal, the arachnoid granulations become active, perhaps explaining earlier experimental findings. Absorption of CSF across brain tissue into capillaries has also been proposed,³³ and according to this theory, the distending force in the production of chronic hydrocephalus is an increased systolic pulse pressure in the brain tissue that is due to decreased intracranial compliance.

9.5 Etiology and Pathophysiology

Hydrocephalus can be a symptom of a large number of disorders: it is associated with tumors and infections and occurs as a complication of prematurity and trauma.^{34–36} It is also seen in apparent isolation. High-resolution MR imaging of postnatal life has provided clues to the etiologies of hydrocephalus, which in the past would have been labeled as idiopathic; some of these include IVH (► Fig. 9.1 A–C), aqueduct stenosis (► Fig. 9.2), and migrational abnormalities.¹⁰ The etiologies of hydrocephalus in one series of pediatric patients are shown in ► Table 9.1.

Hydrocephalus is due to abnormal CSF reabsorption, flow, or rarely overproduction.

The main situation in which CSF production is increased enough to cause hydrocephalus is the presence of a choroid plexus papilloma. These tumors contain functional choroid epithelium and can produce very large amounts of CSF. However, even in such cases, reabsorption is probably defective because otherwise-normal individuals can usually tolerate the elevated CSF production rate of these tumors. CSF accumulation, in turn, leads to raised ICP.

The etiology of hydrocephalus depends upon the age of the child. During the neonatal period to late infancy (0 to 2 years), hydrocephalus is usually caused by perinatal hemorrhage, meningitis, or developmental abnormalities, the most common being aqueduct stenosis. The hydrocephalus seen in babies with spina bifida usually results from an associated Chiari malformation.

In early to late childhood (2 to 10 years), the most common causes of hydrocephalus are posterior fossa tumors and aqueduct stenosis.

9.5.1 Congenital Causes in Infants and Children

Approximately 55% of all cases of hydrocephalus are congenital. Primary aqueductal stenosis accounts for approximately 5% of cases of congenital hydrocephalus, whereas aqueductal stenosis secondary to neoplasm, infection, or hemorrhage accounts for another 5%.³⁴ Primary aqueduct stenosis usually presents in infancy. Its morphology may be that of “forking” of the aqueduct, an aqueductal septum, “true” narrowing of the aqueduct, or X-linked aqueduct stenosis. Bickers-Adams syndrome is an X-linked form of hydrocephalus accounting for 7% of cases in males. It is characterized by stenosis of the

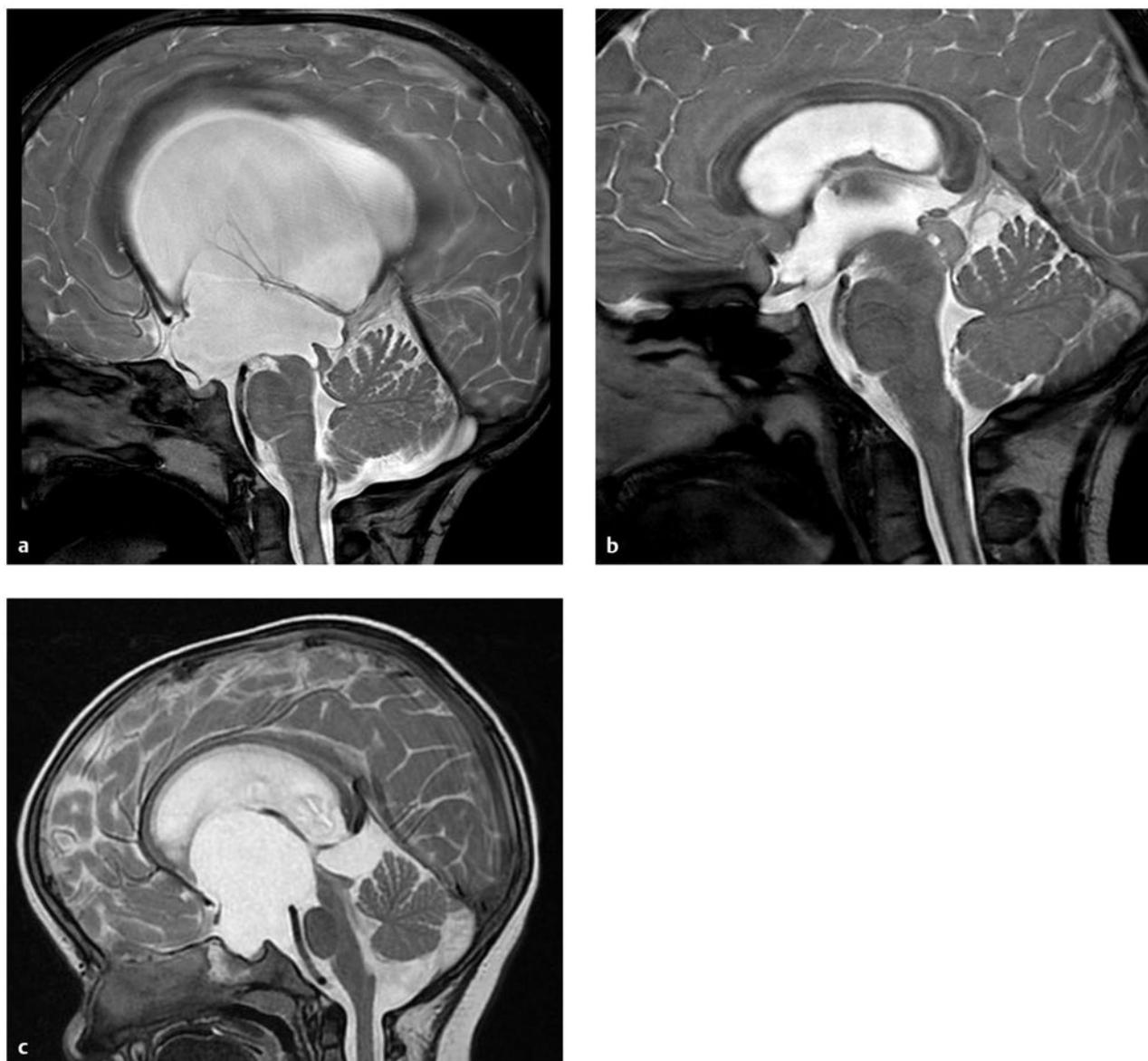


Fig. 9.1 Post-intraventricular hemorrhage (IVH) hydrocephalus. (a) Initial coronal ultrasound showing IVH with extension into parenchyma. (b) Axial magnetic resonance images at two different levels demonstrating slight enlargement of the ventricles. Note immature sulcal development. (c) Coronal ultrasound following progression of hydrocephalus that led to surgical treatment.

aqueduct of Sylvius, severe mental retardation, and in 50% of cases by an adduction–flexion deformity of the thumb. Secondary aqueduct stenosis is due to gliosis secondary to intrauterine infection or germinal matrix hemorrhage.³⁷

Anatomical malformations frequently observed with idiopathic congenital hydrocephalus include Chiari malformations, Dandy-Walker malformation, and others.^{36,38} Dandy-Walker malformation is associated with atresia of the foramina of Luschka and Magendie and affects 2 to 4% of newborns with hydrocephalus. About 50% of all patients with Dandy-Walker malformation develop hydrocephalus. The dilated fourth ventricle does not communicate effectively with the subarachnoid space. In Chiari malformations, hydrocephalus may occur with fourth

ventricle outlet obstruction in Chiari type 1 malformation and is commonly associated with myelomeningocele in Chiari type 2 malformation.

Hydrocephalus occurs in approximately 80 to 90% of patients with myelomeningocele; of these cases, 50% are obvious at birth.^{18,39}

Neonatal hydrocephalus can also be part of a major cerebral malformation, such as an encephalocele or holoprosencephaly, or can be associated with inherited metabolic diseases, such as achondroplasia and Hurler disease. Other causes of congenital hydrocephalus include agenesis of the foramen of Monro, congenital tumors, arachnoid cysts and vascular malformations, and intrauterine toxoplasmosis.

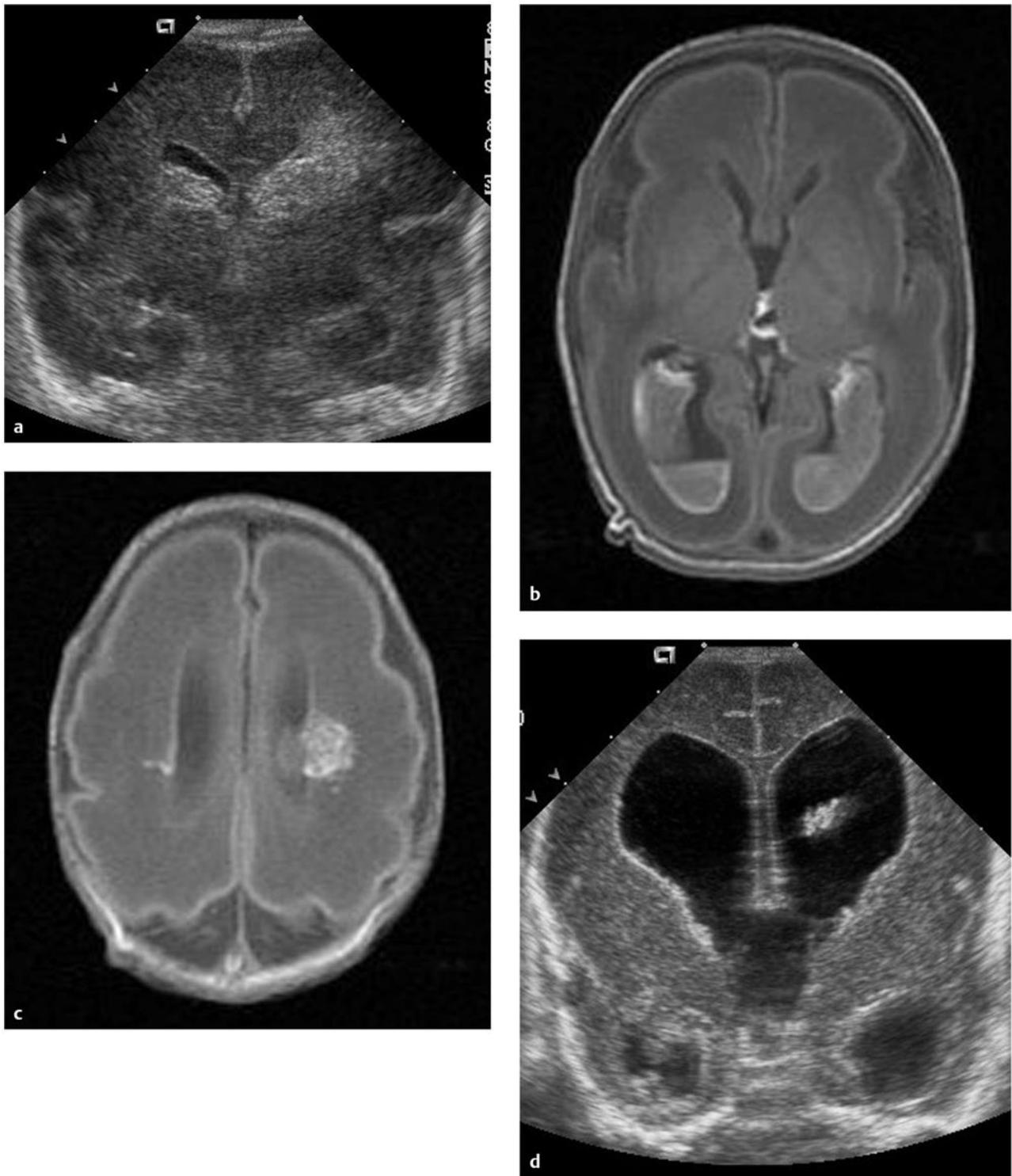


Fig. 9.2 Intrauterine magnetic resonance image of severe hydrocephalus. (a-d) Sequential coronal views.

9.5.2 Acquired Causes in Infants and Children

Infective causes of hydrocephalus include meningitis, especially bacterial, which can lead to hydrocephalus by either inflammatory aqueduct stenosis or leptomeningeal fibrosis. In some

geographic areas, parasitic disease, such as intraventricular cysticercosis, can cause hydrocephalus by mechanical obstruction.

Post-hemorrhagic hydrocephalus occurs following IVH, which can be related to prematurity, head injury, or rupture of a vascular malformation. Communicating hydrocephalus after subarachnoid hemorrhage is more common in adults and is

rarely seen in children. Over the past two decades, there has been remarkable improvement in the survival of extremely low-birth-weight infants; however, the most immature of these infants remain at increased risk for neonatal complications that potentially affect long-term neurologic developmental outcome, including IVH. The risk for severe IVH varies inversely with gestational age, with an overall incidence of 7 to 23%.^{40–42} Approximately one-third of extremely low-birth-weight infants with an IVH develop post-hemorrhagic hydrocephalus, and 15% of them will require shunt insertion.^{43–45}

Hydrocephalus after IVH is usually ascribed to fibrosing arachnoiditis, meningeal fibrosis, and subependymal gliosis, which impair the flow and reabsorption of CSF. Recent experimental studies have suggested that acute parenchymal compression and ischemic damage and increased parenchymal and perivascular deposition of extracellular matrix proteins—probably due at least partly to upregulation of transforming growth factor- β (TGF- β)—are further important contributors to the development of the hydrocephalus. IVH is associated with damage to periventricular white matter,

and the damage is exacerbated by the development of hydrocephalus; combinations of pressure, distortion, ischemia, inflammation, and free radical-mediated injury are probably responsible.⁴⁶

Mass lesions account for 20% of all cases of hydrocephalus in children. These are usually tumors such as medulloblastoma, astrocytoma, and ependymoma, but cysts, abscesses, vascular malformations, or hematomas also can be the cause. Twenty percent of pediatric patients develop hydrocephalus requiring shunting following posterior fossa tumor removal. This may be delayed up to a year. Risk factors for the requirement of CSF diversion in this group include age younger than 2 years, papilledema, enlarged ventricles, presence of metastases, and tumor type.⁴⁷ Increased venous sinus pressure can also lead to hydrocephalus. This can be related to achondroplasia, some forms of craniosynostosis, or venous sinus thrombosis.

Iatrogenic causes of hydrocephalus include hypervitaminosis A, which can lead to hydrocephalus by increasing secretion of CSF or by increasing permeability of the blood-brain barrier. Hypervitaminosis A is a more common cause of idiopathic intracranial hypertension.^{48,49}

Table 9.1 Causes of hydrocephalus

Causes	Percentage of patients
Intraventricular hemorrhage	24.1
Myelomeningocele	21.2
Tumor	9.0
Aqueductal stenosis	7.0
Infection	5.2
Head injury	1.5
Other	11.3
Unknown	11.0
Two or more causes	8.7

Source: Modified with permission from Drake et al, 1998.

9.6 Clinical Characteristics

The clinical features of hydrocephalus depend on the age of the patient at presentation and the time of onset in relation to closure of the cranial sutures. With the current advances in antenatal monitoring, the majority of congenital cases of hydrocephalus are diagnosed early (► Fig. 9.3), allowing planned cesarian delivery in the moderate to severe cases in which cephalopelvic disproportion is expected.

9.6.1 Symptoms and Signs in Infants

Hydrocephalus can present as acute raised ICP, but because of the relative distensibility of the infant skull, the presentation may be more subtle, with failure to thrive and achieve

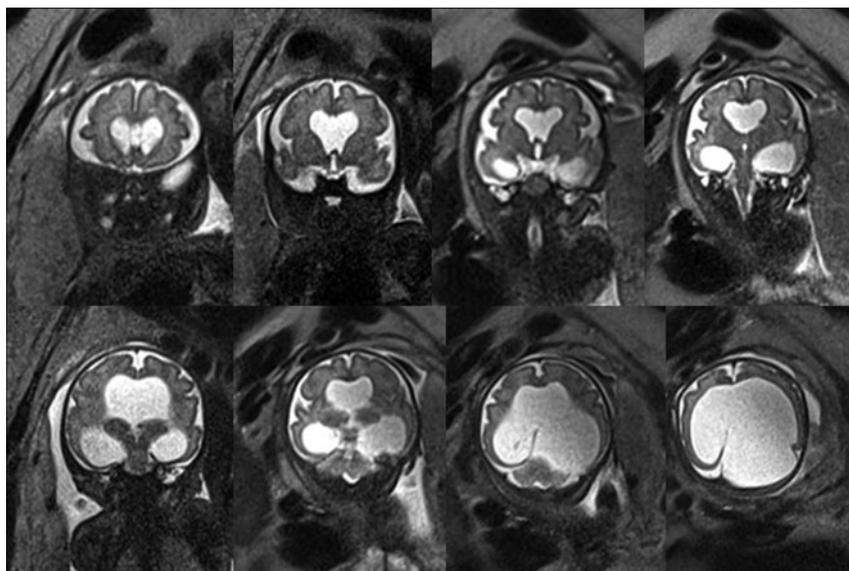


Fig. 9.3 Obstructive hydrocephalus from (a) aqueduct occlusion, (b) tectal glioma, and (c) suprasellar arachnoid cyst.

milestones. Infants with hydrocephalus may be drowsy and irritable. Poor feeding and vomiting are common. These infants may have apneic spells, bradycardia, and a bulging, tense anterior fontanel. Head circumference increases abnormally across centiles: the head circumference is at or above the 98th percentile for age. The scalp veins may be distended, the scalp skin thin and shiny, and the cranial sutures splayed. In the minority of cases, an abnormally large head is present at birth. In most, however, the hydrocephalus only gradually becomes obvious. In advanced cases, clinical examination reveals a significant craniofacial disproportion with expansion of the dome and low-set ears and eyes. In very severe cases, in which the cerebral cortex is thinned, transillumination of the cranial cavity may be possible. Epileptic seizures are rarely seen as a result of hydrocephalus alone.

Papilledema is rare in this age group, although funduscopy may reveal retinal venous engorgement. Oculomotor abnormalities may include abducens nerve palsy. Upgaze palsy from third ventricular pressure on the midbrain tectum, producing a “setting-sun” sign, can be observed, although this is usually absent in premature infants. In babies over the age of 6 months, limb tone may be increased, with spasticity preferentially affecting the lower limbs. However, some infants with definite hydrocephalus exhibit no such signs, as hydrocephalus may have developed slowly and the splaying of the sutures may have prevented the ICP from rising considerably. In fact, some infants with hydrocephalus after intraventricular hemorrhage may show hypotonia.

9.6.2 Symptoms and Signs in Older Children

In older children (older than 2 years), the head circumference is usually within normal limits if hydrocephalus develops after closure of the cranial sutures or may be increased in children with preexisting (infantile) but unrecognized progressive hydrocephalus.

Learning problems and reduced intellectual function are common, and neurologic development may be delayed. School-age children may have deteriorating school performance as a result of headaches, failing mental function, memory loss, or behavioral disturbances. More acutely, these children present with symptoms and signs of increased ICP, such as headache, nausea and vomiting, drowsiness, gait changes, papilledema, and upgaze and/or abducens palsy. Failure of upward gaze is due to pressure on the tectal plate through the suprapineal recess. The limitation of upward gaze is of supranuclear origin. When the pressure is severe, other elements of the dorsal midbrain syndrome (Parinaud syndrome) may be observed, such as light–near dissociation, convergence–retraction nystagmus, and eyelid retraction (Collier sign).

Evidence of abnormal hypothalamic function (e.g., short stature or gigantism, obesity, delayed puberty, primary amenorrhea or menstrual irregularity, and diabetes insipidus) may occur secondary to increased ICP or dilatation of the third ventricle. Difficulty in walking may occur secondary to truncal and limb ataxia or limb spasticity. This affects the lower limbs preferentially because the periventricular pyramidal tract is stretched by the enlarged ventricles.

Neck pain may indicate associated tonsillar herniation, and blurred vision may be present as a consequence of papilledema, which if left untreated leads to optic atrophy.

9.7 Genetics

Although commonly considered a single disorder, human hydrocephalus is a collection of heterogeneous, complex, and multifactorial disorders. A growing body of evidence suggests that genetic factors play a major role in the pathogenesis of hydrocephalus.⁵⁰ Congenital hydrocephalus may occur alone (nonsyndromic) or with other anomalies (syndromic). It is estimated that about 40% of cases of hydrocephalus have a possible genetic etiology.⁵¹

In genetic terms, the isolated (nonsyndromic) form of hydrocephalus is a primary and major phenotype caused by a specific faulty gene. In syndromic forms of congenital hydrocephalus, it is difficult to define the defective gene because of the association with other anomalies. Autosomal-recessive, autosomal-dominant, X-linked recessive,⁵² and X-linked dominant⁵³ forms of hydrocephalus are recognized.

At least 43 mutants/loci linked to hereditary hydrocephalus have been identified in animal models and humans. To date, nine genes associated with hydrocephalus have been identified in animal models, whereas only one such gene has been identified in humans: the hydrocephalus (X-linked) gene.⁵¹ Cases of X-linked hydrocephalus (HSAS1, OMIM) comprise approximately 5 to 15% of the congenital cases with a genetic cause.^{51,54}

The gene responsible for X-linked human congenital hydrocephalus is at Xq28 and encodes L1CAM (L1 cell adhesion molecule).⁵⁵ CRASH (corpus callosum agenesis, retardation, adducted thumbs, shuffling gait, and hydrocephalus) incorporates the L1 mutations that were formerly regarded as multiple separate entities.⁵⁶ Congenital aqueductal stenosis can also be caused by autosomal-recessive mechanisms (OMIM 236635).⁵⁷ In general, the recurrence risk for congenital hydrocephalus, excluding X-linked hydrocephalus, is low. Empiric risk rates range from less than 1% to 4%,⁵⁸ indicating the rarity of autosomal-recessive congenital hydrocephalus.^{51,54,59} However, multiple human kindreds with congenital hydrocephalus have been reported.^{50,51,54,60}

Hydrocephalus has been observed in many mammals.⁵⁰ Review of the molecular etiologies shows a very diverse set of pathogenetic mechanisms. Perturbation of almost any molecule that plays a crucial role in early brain development and the sequential regulation of CSF dynamics may be involved. Hydrocephalus may also be caused by a malfunction of the ependymal cells,⁶¹ mesenchymal cells,^{62,63} growth factor signaling,^{64,65} disruption of extracellular matrix (ECM),^{66,67} and membrane fusion events (synaptosomal-associated protein, or SNAP).⁶⁸

9.8 Imaging Studies

9.8.1 Cranial Ultrasound

Ultrasound is by far the quickest, cheapest, and most convenient method for demonstrating ventricular enlargement in infants with an open fontanel, particularly premature infants

with post-hemorrhagic hydrocephalus, and for serial imaging in follow-up. It is also useful for the diagnosis of intrauterine hydrocephalus. Measurement of ventricular width from the midline to the lateral border of the lateral ventricle in the midcoronal view is the measurement with the least interobserver variability, and centiles for gestational age have been compiled.⁶⁹

No sedation is required for acquiring of ultrasound images, and the procedure can be repeated frequently without any adverse effects. It may not visualize the posterior fossa well and may not always establish an etiologic diagnosis.

9.8.2 Computed Tomography

CT demonstrates the size and morphology of the ventricles and periventricular lucency, and it can reveal underlying pathologies, such as hemorrhage and posterior fossa tumors. Baseline imaging of asymptomatic patients (especially after shunt revision) may serve as a reliable study for comparison with subsequent imaging when patients become symptomatic. CT is widely available in many facilities and often does not require sedation of the child. However, there is mounting concern about the effects of exposure to radiation, so that alternate imaging⁷⁰ultrasound or rapid-sequence MR imaging—is frequently preferred.⁷¹

9.8.3 Magnetic Resonance Imaging

MR imaging provides a better morphological definition and a better etiologic diagnosis, such as the presence of low-grade gliomas or colloid cysts, which may not be demonstrated on CT. It is better for evaluating Chiari malformations and cerebellar or periaqueductal tumors. Cine MR imaging is an MR imaging technique to measure CSF stroke volume in the cerebral aqueduct. This is used for demonstrating the patency of third ventriculostomy fenestration. The limitations of MR imaging are that children often require a general anesthetic and that programmable shunt valves require reprogramming after MR imaging. In patients with acute hydrocephalus characterized by ventricular enlargement and transependymal edema with loss of sulci, the diagnosis is usually very obvious. However, there may be no reliable measurement values that can confirm or exclude the presence of hydrocephalus in a single series of images in some patients. Serial imaging demonstrating an increase in ventricular size may be required in equivocal cases. Conversely, an apparently normal ventricular size cannot exclude active hydrocephalus in a patient with a preexisting shunt, for example. A number of methods have been used to attempt to define hydrocephalus quantitatively on CT or MR imaging studies.⁷² Hydrostatic hydrocephalus is suggested in either of the following situations:

1. Both temporal horns have a width of 2 mm or more and the sylvian and interhemispheric fissures are not visible.
2. Both temporal horns have a width of 2 mm or more and the ratio of the largest width of the frontal horns to the internal diameter from inner table to inner table at this level is greater than 0.5.

Other features suggestive of hydrostatic hydrocephalus include the following: ballooning of the frontal horns of the lateral

ventricles and third ventricle; periventricular hypoattenuation on CT or periventricular high-intensity signal on T2-weighted imaging and fluid-attenuated inversion recovery [FLAIR] sequences on MR imaging, suggesting transependymal exudate or migration of CSF; compression of the sulci and basal cisterns; upward bowing of the corpus callosum and downward displacement of the floor of the third ventricle on sagittal MR imaging. The Evans ratio is the ratio of largest width of the frontal horns to the maximal biparietal diameter. A ratio greater than 30 is suggestive of hydrostatic hydrocephalus. A modification of the Evans ratio, the frontal occipital horn ratio, may be more accurate and has been used in a number of prospective studies to quantify the degree of hydrocephalus and the response to treatment.^{73,74}

9.8.4 Radiologic Criteria for Chronic Hydrocephalus

Skull radiographs may depict erosion of the sella turcica, or a “beaten copper” cranium. The latter can also be seen in craniosynostosis. The temporal horns may be less prominent than in acute hydrocephalus, and the third ventricle may herniate into the sella turcica. The corpus callosum may be atrophic; this is best appreciated on sagittal MR imaging. In infants with chronic hydrocephalus, sutural diastasis and delayed closure of the fontanelles may be seen.

In communicating hydrocephalus, all ventricles are dilated. If the lateral and third ventricles are dilated and the fourth ventricle is small, it is likely that the obstruction is at the level of the aqueduct of Sylvius. MR imaging will help determine the cause, such as defining the presence of an obstructing tumor.

9.9 Diagnosis

Modern ultrasonography and, since the late 1980s, fetal MR imaging have significantly improved the ability to detect ventricular enlargement as a result of hydrocephalus in utero. Antenatal ultrasound and MR imaging provide reasonably detailed fetal brain anatomy, detect malformations, and can detect fetal ventriculomegaly as early as 17 to 21 weeks and 8 to 21 weeks, respectively.^{75,76} Normative data for ventricular size allow serial investigation during gestation.⁷⁷

Anatomical ventriculomegaly is not sufficient to diagnose hydrocephalus. When making a diagnosis of hydrocephalus in neonates or infants, it is essential to establish that there is a truly abnormal rate of skull growth. Recording head circumference and comparing it with body weight and length centile charts are an integral part of the postnatal follow-up of any child. The head circumference must be recorded and plotted on an accepted growth curve chart with the patient's exact age or, in premature infants, the gestational age. In the presence of hydrocephalus, any of the following may be observed: head circumference greater than 2 standard deviations above normal or out of proportion to body length or weight, upward deviations (crossing centile curves), or continued head growth of greater than 1.25 cm per week.

Evaluation of the patient with an enlarged head entails consideration of the many causes of macrocephaly, including hydrocephalus. Evaluation should include a history of trauma or

CNS infection. The family history may demonstrate X-linked hydrocephalus caused by stenosis of the aqueduct of Sylvius or may reveal familial macrocephaly.

After a full review of the pregnancy, delivery, and neonatal history, as well as the clinical examination and ultrasound examination, it is usually possible to classify the hydrocephalus into an etiologic group. If no obvious explanation for the hydrocephalus can be found, then intrauterine infection should be investigated. Coagulation factor deficiency as well as thrombocytopenia should be excluded; isoimmune thrombocytopenia and coagulation factor V deficiency can present as congenital hydrocephalus resulting from congenital IVH.

9.9.1 Differential Diagnosis

Besides hydrocephalus, causes of increasing head size include chronic subdural effusion or hematoma, pseudotumor cerebri, neurofibromatosis, metabolic abnormalities of bone or brain, and cerebral gigantism (Soto syndrome). There are also benign familial forms.

Benign extracranial hydrocephalus is a condition of infants and children in which enlarged subarachnoid spaces are accompanied by increasing head circumference with normal or mildly dilated ventricles. This condition is also known as benign subdural collections of infancy or pericerebral CSF collections. It has been postulated by some to be a variant of communicating hydrocephalus but tends to run a benign course and stabilize by 12 to 18 months of age.⁷⁸⁻⁸⁰ Close serial monitoring of the head circumference and follow-up imaging with CT or MR imaging is recommended to monitor for ventriculomegaly. Shunting is rarely, if ever, required. A rare but striking condition that can mimic hydrocephalus is hydranencephaly, a post-neurulation defect that results in total or nearly total absence of the cerebral tissue; the intracranial cavity is filled with CSF. This is usually due to bilateral internal carotid artery infarcts or infection.⁸¹ Other brain malformations, such as agenesis of the corpus callosum and alobar holoprosencephaly, may also be associated with hydrocephalus but more often represent expansion of the third ventricle and separation of the lateral ventricles. Hydrocephalus ex vacuo is due to atrophy rather than altered CSF dynamics. Certain metabolic and degenerative disorders, such as glycogen storage and Alexander disease, can cause macrocephaly. Brain tumors of infancy may reach an enormous size, producing a large head apart from whether there is associated hydrocephalus. Finally, there may be a family history of large heads.

9.10 Pathology

The precise pathologic features of hydrocephalus vary depending on the age at onset, the rate of ventricular enlargement, and the degree of ventriculomegaly. Typically, elevated CSF pressure initially enlarges the frontal horns of the lateral ventricles, followed by enlargement of the entire ventricular system above the site of obstruction. Hydrocephalus is associated with flattening and destruction of the ventricular ependymal lining as well as edema and necrosis of the periventricular white matter.⁸² Periventricular glial cells proliferate, resulting in a layer of reactive gliosis. The pathologic

findings may be a result of reduction in blood flow to the white matter, causing hypoxic injury, and/or toxicity to the white matter due to the buildup of waste products not removed appropriately because of changes in the extracellular matrix.⁸³

In post-hemorrhagic hydrocephalus, high concentrations of proinflammatory cytokines,⁸⁴ free iron, and hypoxanthine,^{85,86} which can generate highly reactive radicals, have been measured in the CSF.

Separation of the ependymal lining of the ventricles enhances permeability, which increases the edema of adjacent white matter (transependymal fluid absorption). The expanding ventricles flatten the cerebral gyri and obliterate the sulci over the cortical surface. Unless the acute obstruction is relieved, the increasing pressure may hinder cerebral blood flow, cause cerebral herniation, and compromise brainstem function.

The increasing pressure and ventricular enlargement are associated with necrosis of the brain parenchyma. White matter is more vulnerable to destruction than cerebral gray matter in the presence of progressive hydrocephalus.^{87,88} The corpus callosum may also be preferentially affected, with evidence of transcallosal swelling, thickening, or demyelination.^{89,90} These effects do not appear to be associated with cognitive changes or neuropsychological evidence of callosal disconnection.

9.11 Management

The management of hydrocephalus is the most common problem in pediatric neurosurgery. In infants and children with symptomatic or progressive ventriculomegaly, the decision to treat with a CSF diversion procedure poses no therapeutic dilemma. However, not all patients with enlarged ventricles require treatment.

In patients with obstructive hydrocephalus secondary to a mass that is surgically accessible, resection of the mass may lead to resolution of the hydrocephalus, and a shunt may not be necessary. This situation occurs infrequently in comparison with communicating hydrocephalus. If no documented obstruction or operable lesion is present and the hydrocephalus is slight and slowly progressive, a trial period of observation or medical management may be indicated, especially in preterm infants.

Another situation in which observation is reasonable is arrested hydrocephalus, which is an uncommon state of chronic hydrocephalus in which the CSF pressure has returned to normal and there is no pressure gradient between the cerebral ventricles and the brain parenchyma. Patients should be followed carefully with neurologic examinations, neuropsychological assessments, and careful assessment of their development. A shunt will be necessary if there is any deterioration of those parameters.

Rapid-onset hydrocephalus with increased ICP is an emergency. Depending on the specific case, any of the following procedures can be performed: ventricular tap in infants; external ventricular drainage and lumbar puncture in post-hemorrhagic and post-meningitic hydrocephalus; endoscopic third ventriculostomy; and ventriculoperitoneal shunt.

The management of patients with in utero hydrocephalus remains controversial. Although the results of surgical attempts in

the 1980s were seen to be ineffective, interest remains as diagnostic technology and fetal surgery techniques advance.⁹¹ The recent Management of Myelomeningocele Study (MOMS), in which patients with a fetal diagnosis of myelomeningocele were randomized to either in utero closure or expectant treatment and postnatal closure, showed a significant increase in the requirement for CSF diversion, from 98 to 68%, albeit with the increased risk for preterm labor and maternal complications.⁹²

9.12 Prognosis

Before the 1950s, the outlook for patients with untreated hydrocephalus was extremely poor. Forty-nine percent of patients had died by the end of the 20-year observation period, and only 38% of survivors had an IQ greater than 85.⁹³ The development of satisfactory shunting substantially improved the outlook for patients with hydrocephalus but brought its own set of problems and complications. Most children with hydrocephalus require multiple shunt revisions. Shunt dependence carries with it an annual mortality rate of 1%.^{94,95} Another series, with 907 patients, reported a mortality rate of 12% at 10 years,⁹⁶ with the main risk factor for death being a history of shunt infection.

Shunt-related complications, including death, have been reported to be greater in patients with myelomeningocele than in those who required shunt placement for the treatment of other conditions.^{39,94}

The neurologic and intellectual disabilities of patients with hydrocephalus depend on many factors, including the etiology and severity of the hydrocephalus, thickness of the cortical mantle and corpus callosum,⁹⁷ requirement for a shunt, and presence of other brain anomalies.⁹⁸ Associated conditions, such as IVH, CNS infection,⁹⁶ and hypoxia, may dictate the ultimate prognosis more than the hydrocephalus.

A series of 233 patients with congenital hydrocephalus were evaluated for longer than 20 years; 13.7% died. The average number of shunt revisions was 2.7. In this series of 233 patients, of 115 who underwent psychological evaluation, approximately 63% showed normal performance, whereas 30% had mild retardation and 7% had severe retardation.⁹⁹ Another study found that children with congenital hydrocephalus were less likely to require special education placement (29%) than were those in whom hydrocephalus was due to meningitis (52%) or IVH (60%).¹⁰⁰

Epilepsy also is more prevalent among patients with hydrocephalus, and complications of shunt surgery appear to play a relatively minor role in its development.¹⁰¹

Intellectual sequelae include significant scatter among Wechsler Intelligence Scale for Children-Revised (WISC-R) subtest scores, often with greater impairment of performance and motor tasks, as well as of nonverbal compared with verbal skills.¹⁰² Normal intellectual function is present in 40 to 65% of patients who receive appropriate treatment.⁹⁸ The probability of normal intelligence is enhanced if shunts are placed early and proper function is maintained. A study of 99 children ranging in age from 6 to 13 years with shunted or arrested hydrocephalus demonstrated a close correlation between area of the corpus callosum affected and impairment of nonverbal cognitive skills and motor abilities.¹⁰³ Behavioral problems also are more common in children with hydrocephalus, irrespective of etiology.¹⁰⁴

9.13 Conclusion

Pediatric hydrocephalus is a common, complex, and in many ways poorly understood disorder. Although the persistent efforts to improve upon the treatments developed over the last century have had modest success, recent advances in imaging, neurophysiology, and molecular biology have led to important discoveries, suggesting that significant advances are imminent.

Pearls

- Hydrocephalus is a deceptively complex disorder, and simplistic explanations or theories have progressively fallen by the wayside.
- The arachnoid granulations are probably not the primary source of CSF absorption in humans—most likely the nasal lymphatics are.
- Try to establish the cause of hydrocephalus in all cases. It may affect treatment decision making, family counseling, prognosis, and outcome.
- Enlarged ventricles do not automatically invoke a shunt or third ventriculostomy. Be sure the risks of a lifelong commitment to an imperfect shunt device or the risks of a third ventriculostomy opening (and potential closure) are truly worth the benefits.

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10 Treatment of Hydrocephalus with Shunts

Ricky Raj S. Kalra and John Kestle

Since the invention of the first implantable shunt valve by Nulsen and Spitz 60 years ago,¹ there have been innumerable innovations and new designs of shunt equipment to treat pediatric hydrocephalus. Shunts have made a dramatic impact on a previously devastating disease; however, despite the rational and seemingly more physiologic designs of these new devices, complications related to ventriculoperitoneal (VP) shunts continue to plague children with hydrocephalus. It is hoped that continued basic and clinical research will lead to advances in the management of pediatric hydrocephalus and improve the quality of life of affected children and their families.

10.1 Epidemiology

The management of hydrocephalus with cerebrospinal fluid (CSF) shunts is the most common neurosurgical problem encountered in the pediatric age group. Based on the Kids' Inpatient Database, the Hydrocephalus Clinical Research Network estimated 38,200 to 39,900 admissions, 391,000 to 433,000 hospital days, and total hospital charges of \$1.4 to \$2.0 billion for pediatric hydrocephalus.² Clearly, the treatment of hydrocephalus with shunts carries significant costs to patients, families, health care centers, and funding organizations.

10.2 Clinical Presentation

The various symptoms associated with hydrocephalus are discussed in Chapter 7. In this chapter, we discuss the criteria used in the determination of treatment for children with hydrocephalus, specifically in relation to CSF shunt insertion.

First-time shunt insertion is predominantly performed by pediatric neurosurgeons. In the International Society for Pediatric Neurosurgery (ISPN) database, 73% of patients who presented for first-time shunt insertion (774 patients) were 6 months of age or less at time of insertion.⁴ Furthermore, the median corrected age of patients entered in the Shunt Design Trial (SDT) was 55 days.⁵ In the endoscopic shunt insertion trial (ESIT), the median corrected age of patients was less than 3 months.⁶ The clinical characteristics of the patients undergoing first-time shunt insertion who were enrolled in SDT are outlined in ► Table 10.1 and ► Table 10.2. The most common causes for hydrocephalus were IVH, myelomeningocele, and brain tumors.

10.2.1 Diagnostic Tests

The decision to treat hydrocephalus is usually precipitated by the observation of ventricular enlargement. In the baby with an open fontanel, ultrasound will quite readily determine whether there is obvious ventriculomegaly. The addition of computed tomography (CT) or magnetic resonance (MR) imaging to the evaluation will vary depending on the center and the clinical characteristics of the patient being considered. Most surgeons prefer to obtain CT scans or MR images before shunt insertion to assess the morphology of the ventricles (including cysts and compartments) and the condition of the surrounding brain. The

exception is hydrocephalus associated with myelomeningocele; some surgeons will place shunts in these patients based on the ultrasound findings alone.⁵

Ventriculomegaly may be due to hydrocephalus or atrophy of surrounding brain tissue. The differentiation between these two conditions is crucial in deciding to place a shunt. Increasing head circumference or signs of raised intracranial pressure (ICP) make the differentiation straightforward. In more difficult cases, several imaging characteristics may help. The radiographic parameters that suggest hydrocephalus rather than atrophy include the following⁷:

- Dilated temporal horns
- Enlarged anterior and posterior recesses of the third ventricle
- Downward displacement of the floor of the third ventricle
- Dilatation and rounding of the frontal horns
- Effacement of the sulci
- Periventricular interstitial edema

In addition, inferiorly displaced cerebellar tonsils seen on sagittal MR imaging may indicate raised ICP.

10.3 Indications for a Shunt

Although the management of hydrocephalus is the most common clinical problem in pediatric neurosurgery, the decision to insert a shunt can be one of the most difficult. In the management of hydrocephalus and shunts, the old adage "If it ain't broke, don't fix it"⁸ is well worth keeping in mind.

Ventriculomegaly, either in a baby who presents with irritability, vomiting, a full fontanel, splayed sutures, and increasing head circumference or in an older child who presents with headache, vomiting, and papilledema, poses no therapeutic dilemma. Such children have raised ICP in need of treatment.

Table 10.1 Etiology of hydrocephalus

Etiology of hydrocephalus	Percentage
Intraventricular hemorrhage	24
Myelomeningocele	21
Brain tumor	9
Aqueductal stenosis	7
Cerebrospinal fluid infection	5
Head injury	2
Two indicated	9
Other	shun
Unknown	12

Source: From Kestle JRW, Garton HJL, Drake JM. Treatment of hydrocephalus with shunts. In: Albright L, Pollack I, Adelson D, eds. Principles and Practice of Pediatric Neurosurgery. New York, NY: Thieme Medical Publishers;1999:76.⁹⁴ Republished with permission.

Table 10.2 Preoperative features of children with hydrocephalus

Symptoms	Percentage	Signs	Percentage	Preoperative imaging	Percentage
Irritability	27	Increased head circumference	81	Magnetic resonance	23
Nausea and vomiting	19	Bulging fontanel	71	Computed tomography	57
Headache	18	Delayed development	21	Ultrasound only	20
Lethargy	18	Loss of upward gaze	16		
New seizure or change in seizure pattern	7	Decreased level of consciousness	13		
Diplopia	6	Papilledema	12		
Worsening school performance	4	Sixth nerve palsy	5		
		Hemiparesis	4		
		Fever	3		
		Nuchal rigidity	2		
		Other neurologic deficit	12		

Source: From Kestle JRW, Garton HJL, Drake JM. Treatment of hydrocephalus with shunts. In: Albright L, Pollack I, Adelson D, eds. Principles and Practice of Pediatric Neurosurgery. New York, NY: Thieme Medical Publishers;1999:76.⁹⁴ Republished with permission.

Other children, however, often present with milder symptoms and signs, or unimpressive imaging studies. In these patients, the decision is more difficult. Several terms are used to describe such children, and a wide range of recommendations can be gleaned from the literature. Some authors believe that asymptomatic mild or moderate ventriculomegaly does not need treatment. The definition of symptomatic, therefore, becomes very important; it is here that opinions vary. This is further complicated by the fact that the decision to place a shunt is often made when the child is very young (in the hope of maximizing cognitive development as the child grows and develops) and subtle cognitive problems are difficult to detect.

Fouyas et al used ICP monitoring to assess 18 patients previously without shunts ages 1 to 15 years (mean, 4.1 years) in whom the diagnosis of hydrocephalus was suspected but uncertain.⁹ The patients presented with developmental delay, deteriorating gait, increasing head circumference, headaches, irritability, or decreasing visual acuity. The clinical findings (examinations sometimes were repeated on several occasions) combined with ultrasound, CT, and MR imaging (done in some) had failed in all cases to reveal an unequivocal need for a shunt. ICP was elevated in 9 of 18 patients, and all of these patients improved symptomatically after shunt placement. The other nine patients had normal pressure and did not undergo shunt insertion. Three of them had a spontaneous resolution of symptoms with observation; the remaining six had persistent symptoms. Whittle et al reported the results of ICP monitoring in 46 children with a clinical and radiographic diagnosis of “arrested” hydrocephalus.¹⁰ The 16 patients that had never had shunts placed (ages 1 to 15 years; mean, 6.0 years) presented with either delayed milestones or decreased school performance ($n=4$), new or unstable seizure disorders ($n=6$), behavioral changes ($n=2$), or no symptoms (i.e., incidental finding; $n=4$). Of these 16 patients, 10 (69%) had elevated ICP. In a subset of children who underwent IQ testing, 2 of 5 with stable serial scores had elevated ICP, whereas 8 of 9 with falling scores had elevated ICP. The authors concluded that many patients with

apparent arrest of hydrocephalus in fact have an insidiously progressive disorder. Overall, however, ICP elevations were just as likely in the completely asymptomatic group as in the group with evidence of cortical dysfunction.

McLone et al defined compensated hydrocephalus as untreated hydrocephalus that is clinically and radiographically stable.^{11,12} In such patients, a variety of imaging studies and invasive tests (e.g., infusion tests, radionuclide studies, ICP monitoring, and Doppler imaging) have been proposed to differentiate which children with apparently asymptomatic ventricular enlargement would benefit from shunt placement. Children who are older than 5 years with a stable clinical course and ventricle size may be monitored without a shunt, but they do require frequent testing of their intellectual development. Children who are younger than 5 years old, particularly those younger than 3 years old, who have anything more than mild hydrocephalus should have shunts placed. This younger group is difficult to assess for intellectual development, and mere attainment of developmental milestones is insufficient to determine ultimate intellectual function.^{11,12} Measurement of opening pressure may be helpful in some cases.

Dias et al conducted a survey study to analyze the threshold for pediatric neurosurgeons to place shunts in asymptomatic children with ventriculomegaly.¹³ The majority of respondents, who represented approximately 25% of full-time practicing pediatric neurosurgeons in North America, considered themselves relatively conservative when it came to shunt placement. Across the 22 scenarios presented, however, there was significant variability in the responses to certain cases, especially those in which developmental delays and head circumference were considered abnormal. The study concluded that the overall threshold for shunt placement was high, but significant treatment variability existed when it came to vague cases.

MR spectroscopy has been suggested as a method of differentiating atrophy from hydrocephalus. Brain lactate levels were more commonly elevated and ratios of *N*-acetyl aspartate to creatine were lower in children with atrophy than in those with

hydrocephalus; however, three of five patients in the atrophic group had inborn errors of metabolism, possibly accounting for some of the metabolic abnormalities seen.¹⁴

Preterm infants with IVH pose another dilemma in regard to CSF diversion. There are few randomized studies to support surgical indications for temporizing devices, such as reservoirs and subgaleal shunts, and similarly limited data for shunt placement. Riva-Cambrin et al analyzed four large pediatric centers to determine whether clinical and radiologic factors influenced practice patterns and treatment modalities.¹⁵ The study evaluated 110 neonates with grade 3 or 4 IVH treated surgically. Thirty-seven patients underwent permanent shunt placement at a mean gestational age of 39.5 weeks. Seventy-three patients (66%) were treated with temporizing devices, and in 65 (89%) of those, the temporizing devices were converted to permanent shunts. The only factors statistically significant in determining placement of a temporizing device were bradycardia episodes, full fontanel, and splayed cranial sutures. Factors associated with conversion to a shunt included a full fontanel and increased ventricular size. Overall, no clear factors aside from bradycardia and ventriculomegaly were significant in determining conversion of temporary to permanent implants. Furthermore, the authors described a “center effect” in determining whether patients underwent a temporizing procedure.

In summary, particularly difficult cases may require ICP monitoring or other adjunctive tests in the assessment of possible hydrocephalus, but in most children, the decision can be based on observation over time. Documentation of a progressive pro-

blem is a key factor in the decision (► Fig. 10.1). This may include progressive developmental or cognitive delay. The most difficult decision is in the young child with compensated hydrocephalus and moderate to severe ventriculomegaly. Further research in this group of children is needed. Additionally, there is significant variability among surgeons and centers in treatment modalities and practice patterns, and thus a greater effort must be devoted to establishing treatment protocols based on randomized and well-evaluated data.

10.3.1 Disease-Specific Considerations Posttraumatic Ventriculomegaly

What is the best management of a 13-year-old child who, after experiencing a closed head injury at 10 years of age, has a history of development delay and MR images showing enlarged ventricles? The child’s rehabilitation physician asks whether a shunt would facilitate recovery. This case presents a rare complication of head injury in pediatrics; however, it is a good example of a case that requires the differentiation of atrophy from hydrocephalus.

Marmarou et al monitored 75 patients whose head injuries resulted in a Glasgow Coma Scale (GCS) score of 8 or less.¹⁶ According to the size of the frontal horns, the ICP, and the resistance to CSF absorption (measured with a lumbar infusion test), the authors classified patients as having normal ICP, benign intracranial hypertension, atrophy, normal-pressure hydrocephalus, or high-pressure hydrocephalus. They advocated placing

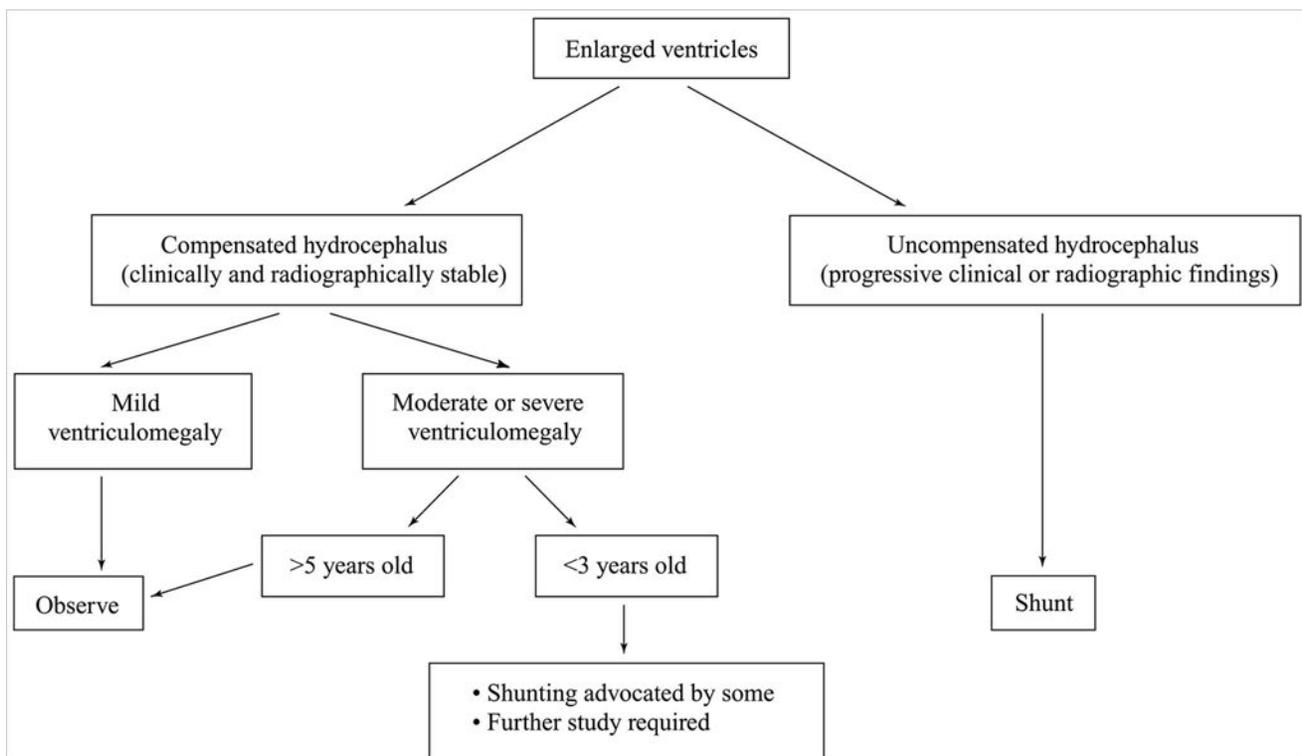


Fig. 10.1 Selection of patients for shunt insertion. (From Kestle JRW, Garton HJL, Drake JM. Treatment of hydrocephalus with shunts. In: Albright L, Pollack I, Adelson D, eds. Principles and Practice of Pediatric Neurosurgery. New York, NY: Thieme Medical Publishers; 1999:75–91.94 Republished with permission.)

shunts in patients in the last two groups; 4 of 15 such patients had shunts placed. All four improved one level on the GCS. In their patients, distention of the temporal horns or third ventricle and periventricular lucency were not specific for hydrocephalus (as they defined it). Subarachnoid hemorrhage on the baseline scan was more common (70% vs. 16%) in patients with hydrocephalus.

Posterior Fossa Tumor

Routine preoperative shunt placement in patients with tumor is no longer common practice because many patients remain shunt-free after tumor removal. Dias and Albright reported a series of 58 patients with posterior fossa tumors and hydrocephalus.¹⁷ Of these, 25 had shunts placed preoperatively, 17 had external ventricular drains (EVDs), and 16 had no preoperative ventricular catheterization. Of the 33 patients without preoperative shunt placement, 24 remained shunt-free at long-term follow-up. When a Cox regression model was used, two factors were associated with shunt insertion: subtotal tumor resection and incomplete dural closure at surgery.

Lee et al studied 42 children (younger than 20 years old) with newly diagnosed posterior fossa primitive neuroectodermal tumors who did not have shunts at the time of surgery and who survived the perioperative period.¹⁸ Of these, 17 (40%) required a shunt by 4 weeks postoperatively, and an additional 2 patients required late shunt placement at the time of tumor recurrence. The group with shunts was younger (5.4 years vs. 10 years), had more severe hydrocephalus, and had more extensive tumor.

At present, a shunt should be withheld in the preoperative phase unless a significant delay between presentation and surgery is expected. Even then, a temporary EVD or a third ventriculostomy may be preferable to a shunt. Many children with a posterior fossa tumor have resolution of their hydrocephalus with tumor removal alone.

At Primary Children's Medical Center, our practice is to insert an EVD at the time of tumor removal. We avoid placing ventricular drains before surgery because of the risk for upward herniation. If the patient's clinical condition requires immediate placement of an EVD, our practice is to proceed with tumor removal at that time. The drain is left at 10 to 15 cm above the head for the first 48 hours postoperatively. The EVD is then gradually elevated over the next 3 to 5 days, clamped, and removed if the child remains well. CT to assess ventricular size with the drain clamped is often useful just before EVD removal.

Sainte-Rose et al have reported their results of the management of hydrocephalus in a consecutive group of 206 children with posterior fossa tumors.¹⁹ Only 4 of 67 patients (6%) who underwent preoperative third ventriculostomy developed progressive hydrocephalus requiring treatment, compared with 22 of 82 patients (28%) who had conventional treatment preoperatively. This is interesting but in our opinion does not justify the risk of doing a preoperative third ventriculostomy in all patients with posterior fossa tumor because a significant number will not need any treatment for hydrocephalus. An endoscopic third ventriculostomy may be considered for patients who appear drain-dependent after tumor removal, but in our experience, most of these patients eventually require a VP shunt.

Riva-Cambrin et al reported a model for assessing the risk of developing hydrocephalus in pediatric patients with posterior

fossa tumors.²⁰ They examined 343 patients with posterior fossa neoplasms and identified predictors of hydrocephalus at 6 months after resection. The preoperative predictors included in the model were age less than 2 years, presence of papilledema, preoperative moderate or severe hydrocephalus, cerebral metastasis, and tumor pathology. A probability scale was developed and validated to predict the need for CSF diversion based on the number of preoperative predictors present.

Myelomeningocele

Several studies are available regarding the timing of shunt placement in children with a myelomeningocele. The reported advantages of simultaneous shunt insertion and back closure are a shorter hospital stay and a decreased incidence of back wound problems.²¹ The disadvantages of simultaneous surgery are increases in the infection rate and the failure rate of the shunt. There is also the risk of committing some children to a shunt who may have not needed one. At present, both approaches are used, and a clear advantage of one over the other has not been demonstrated.

Caldarelli et al compared simultaneous shunt placement with delayed shunt placement in 89 children with myelomeningocele treated between 1980 and 1994.²² The 1-year failure rates in the simultaneous and delayed shunt insertion groups were 31% and 47%, respectively; infection rates were 23% and 7%. Six patients had a shunt inserted first and underwent delayed back closure; 5 of them (83%) had a shunt infection. At the University of Pittsburgh, 69 patients with myelomeningocele underwent back closure and either simultaneous ($n=21$) or delayed ($n=48$) shunt placement between 1987 and 1993.²¹ The two groups were similar in terms of head circumference, but no other comparative information was given. There were 8 children with CSF leak from the lumbar wound in the delayed group and none in the simultaneous group. The rate of obstruction, however, was higher in the simultaneous group, so the overall complication rate was not significantly different between the groups. The infection rate was not different between the groups (1 of 21 and 2 of 48). The authors concluded that simultaneous repair led to shorter hospitalizations and lower rates of back wound morbidity.

Adzick et al published a landmark study comparing prenatal and postnatal repair of myelomeningoceles in regard to primary outcomes, including mortality and the need for a CSF shunt.²³ They reported that 40% of infants who underwent intrauterine closure of the myelomeningocele required shunt placement by 12 months, whereas 82% of the patients who underwent postnatal repair required a shunt by 12 months. The study concluded that prenatal closure of myelomeningocele increased fetal, pregnancy, and delivery risk but resulted in a lower need for shunt placement. Secondary outcomes also showed improved motor scores for patients with intrauterine repair.

10.3.2 Shunt Versus Third Ventriculostomy

Once a diagnosis of hydrocephalus has been made and treatment is required, a choice must be made between a shunt and a third ventriculostomy. As is discussed in the next chapter, on neuroen-

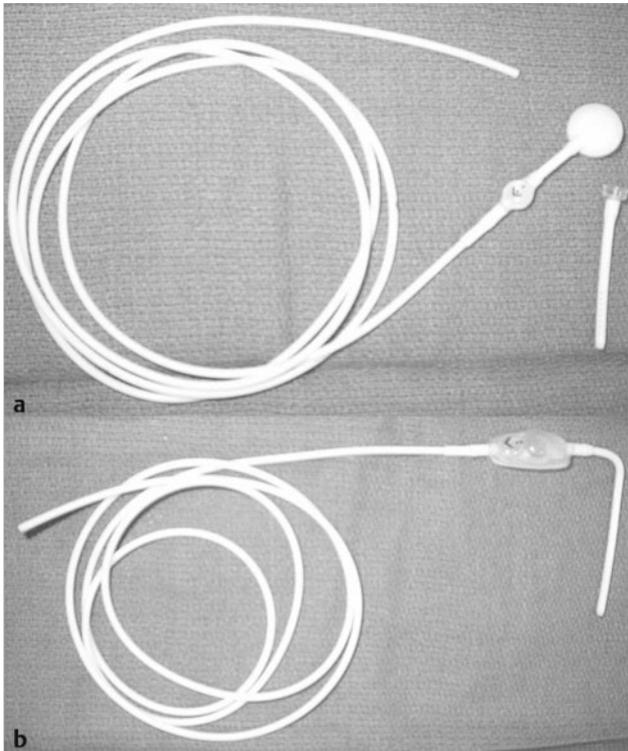


Fig. 10.2 Shunt systems typically contain three parts: a ventricular catheter, a valve with or without a reservoir, and distal tubing. (a) They are available as separate components or (b) unitized.

doscopy, several patients with previously placed shunts are now being treated with endoscopic third ventriculostomy. Ideal patients for third ventriculostomy have evidence of noncommunicating, or obstructive, hydrocephalus and preservation of CSF absorption. Unfortunately, patient selection remains a challenge because there is no simple, noninvasive test to assess the adequacy of CSF absorption. In general, patients who have late-onset hydrocephalus from aqueductal stenosis do the best after third ventriculostomy, presumably because they had normal CSF absorption before blockage at the aqueduct. The surgical goal is to create an opening in the floor of the third ventricle between the infundibular recess and the mammillary bodies. This creates a free-flowing communication between the ventricular system and the basal subarachnoid spaces. Endoscopic third ventriculostomy is an option for about a quarter of children with hydrocephalus. The remaining majority, however, will still require a shunt.

10.4 Equipment

VP shunts are composed of three basic elements: a ventricular catheter, a valve, and a peritoneal catheter (► Fig. 10.2). There are many variations of each of these components available on the market.

10.4.1 Ventricular Catheter

Barium-impregnated Silastic (Dow Corning, Midland, MI) tubes that enter the ventricle are available in several configurations.

Several transverse diameters are available, but the difference is primarily in the wall thickness because the internal diameters are almost identical. Right-angled ventricular catheters are also available, but they are somewhat limiting because the intracranial length is fixed. If right-angled catheters are used, it is necessary to have several catheters of different lengths available for different clinical situations. Ventricular catheters with flanged tips were thought to minimize proximal obstruction, but this has not been supported in the literature.^{24,25}

Another consideration is whether the ventricular catheter should be a separate or integral part of the valve mechanism. When the ventricular catheter is inserted, if bleeding occurs, it is best to allow drainage of fluid through the ventricular catheter before attaching it to the valve. With an integral ventricular catheter and valve, this is not possible; the blood and cellular debris can occlude the valve immediately. For this reason, we use a separate ventricular catheter.

Recent advances in ventricular catheter development have included antibiotic-impregnated proximal catheters. In prospective trials, the clindamycin- and rifampin-impregnated catheters (Bactiseal; Codman & Shurtleff, Raynham, MA) have been shown to provide antistaphylococcal coverage.

10.4.2 Valves

As outlined previously, most modern valves can be grouped into one of several categories based on their hydrodynamic characteristics^{24,26}: differential-pressure valves, siphon-resisting valves, flow-regulating valves, and adjustable valves (► Fig. 10.3 and ► Fig. 10.4).

Differential-Pressure Valves

Differential-pressure valves have been available longer than the other valves, and surgeons have accumulated the most experience with this type of valve. These valves open when the pressure difference across the valve exceeds a predetermined threshold. The valve then remains open, and during this time it has a very low resistance to flow. When the pressure difference drops below the predetermined threshold, the valve closes again and flow stops. When the patient is in the upright position, a large differential pressure between the head and the abdomen develops from the long column of water in the shunt tubing. The valve therefore opens, and fluid flows until the pressure in the head is excessively negative.²⁷ This phenomenon is called siphoning, and it is thought to be responsible for overdrainage and its associated complications (► Fig. 10.5).

Differential-pressure valves are available with low, medium, and high opening pressures. In general, low-, medium-, and high-pressure valves refer to opening pressures of approximately 5, 10, and 15 cm H₂O, respectively. Unfortunately, however, there are no uniform standards for these designations, and the manner in which the pressure is measured is variable. Furthermore, the large column of fluid and the associated negative pressure overwhelm the differences among these three pressures when the patient assumes the upright position. Drake and Sainte-Rose have reviewed the many brands and configurations of differential-pressure valves.²⁴

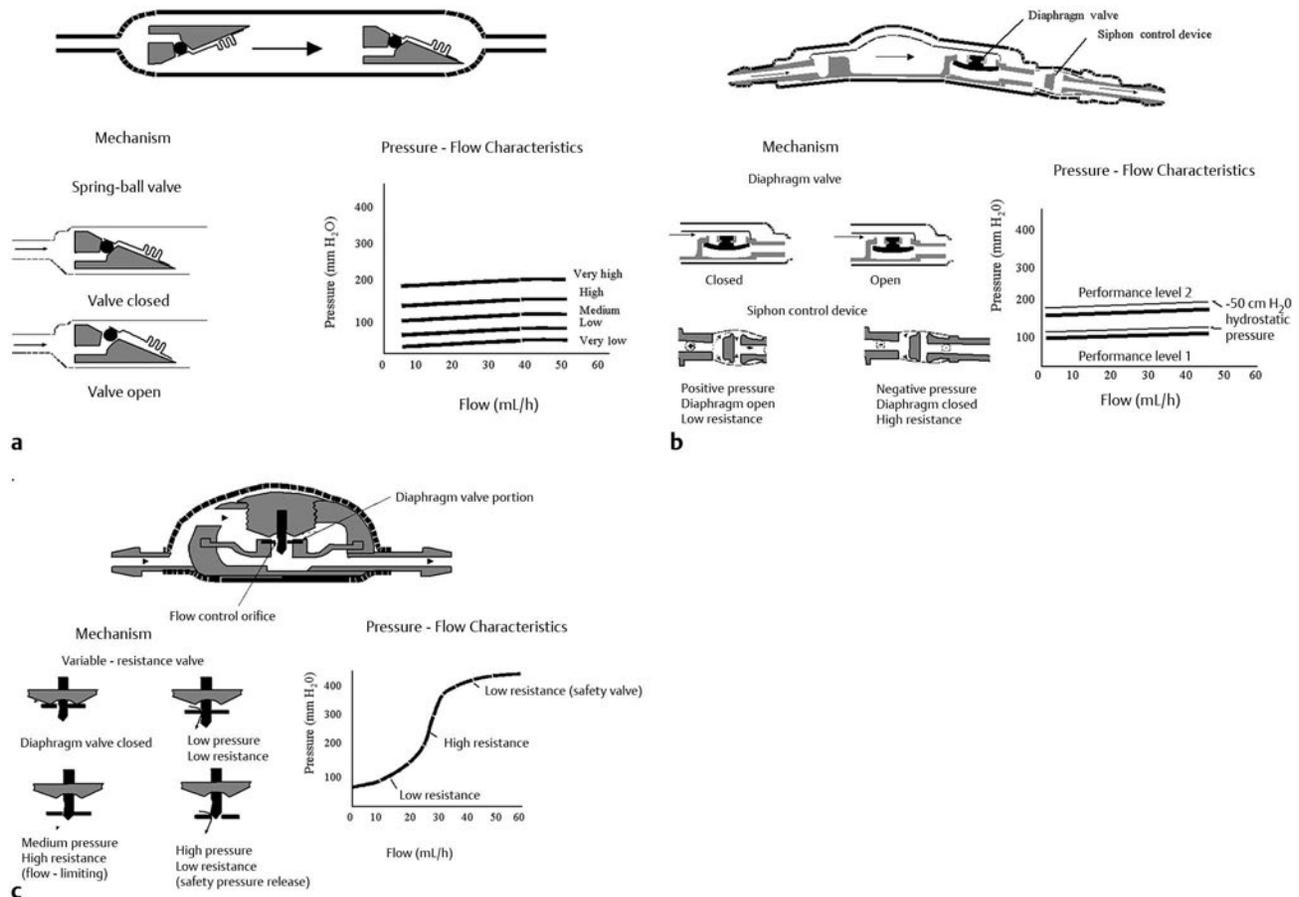


Fig. 10.3 Standard shunt valve designs. In a standard differential-pressure valve (a), flow increases rapidly once the opening pressure is exceeded. The PS Medical Delta (Medtronic Neurosurgical) valve (b) consists of a standard differential-pressure valve (diaphragm type) followed by an antisiphon device to reduce the effects of gravity when the patient is upright. The Orbis Sigma (Cordis Corporation) valve (c) is a flow-limiting valve. (From Drake JM, Kestle JRW. Determining the best cerebrospinal fluid shunt valve design: the pediatric valve design trial. *Neurosurgery* 1996;38:605. Republished with permission.)

Siphon-Resisting Valves

The Delta valves (Medtronic Neurosurgical, Goleta, CA) contain a device that is designed to reduce flow as the patient assumes the upright position (i.e., when siphoning occurs). Similar mechanisms are available as separate components that can be added to other shunt systems (e.g., Mueller Heyer-Schulte anti-siphon device [Integra, Plainsboro, NJ] and Medtronic Neurosurgical siphon control device).

Flow-Regulating Valves

The Orbis Sigma valve (Cordis Corporation, Bridgewater, NJ) consists of a flexible diaphragm that moves along a piston of variable diameter, resulting in three pressure flow stages. In stage 1, the valve functions like a differential-pressure valve. In stage 2, as the ventricular pressure increases, the diaphragm descends along the piston, whose diameter progressively enlarges. This reduces the flow orifice and dramatically increases the resistance to flow. A very small increase in the flow rate results despite a progressive increase in pressure. In stage 3, a high-pressure safety release mechanism results in open flow

when the pressure in the ventricular catheter reaches approximately 40 cm H₂O. The diaphragm at this point is beyond the end of the piston and resistance is very low.

Externally Adjustable Valves

More recently developed shunt systems have incorporated an adjustable valve, which enables the surgeon to make non-invasive alterations in the valve's pressure-flow profile as the patient's clinical course changes.²⁸⁻³³ Unlike traditional valves, however, programmable valves may be percutaneously adjusted with an external magnet or a special programming tool that works via a magnetic field.^{34,35} This may be advantageous in patients with normal-pressure hydrocephalus, in patients with arachnoid cysts, and in patients with complications caused by acute or chronic overdrainage, such as subdural hygromas, chronic subdural hematomas, and slit-ventricle syndrome (SVS).³⁶ In pediatric patients, closure of the sutures, attainment of erect posture, growth, and aging are all additional situations in which the opening pressure of the valve may require adjustment.³³ A randomized clinical trial did not demonstrate any survival benefit of the

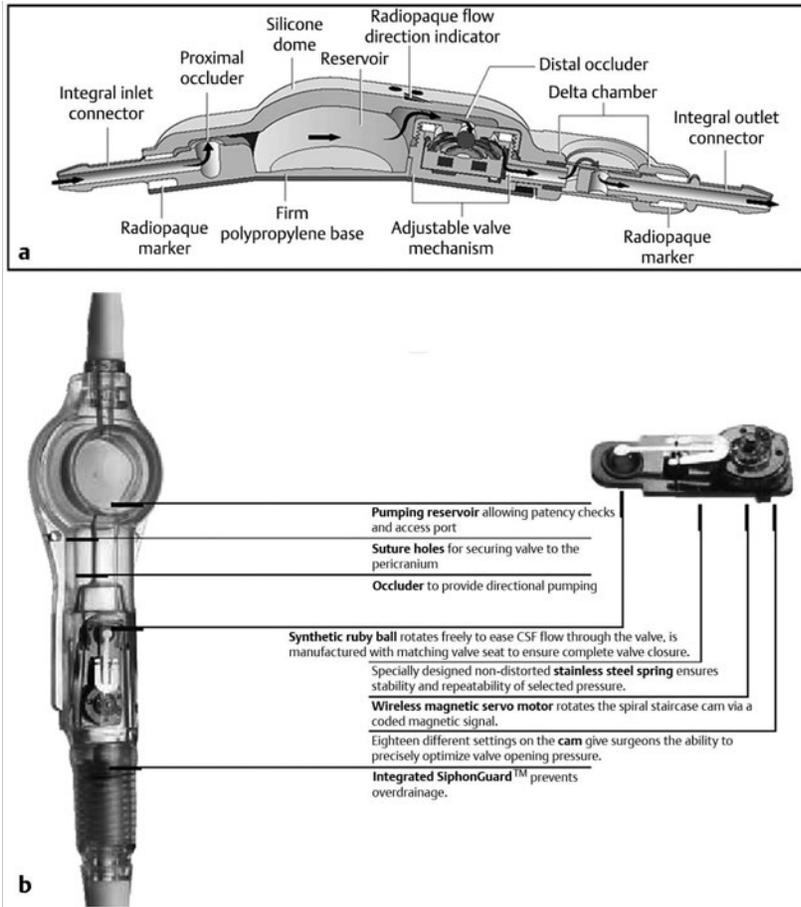


Fig. 10.4 Programmable shunt valve designs. Both the (a) Strata (Medtronic Neurosurgical) and (b) the Codman-Medos (Codman & Shurtleff) valves allow percutaneous adjustment of the valve pressure with an external magnetic tool. CSF, cerebrospinal fluid.

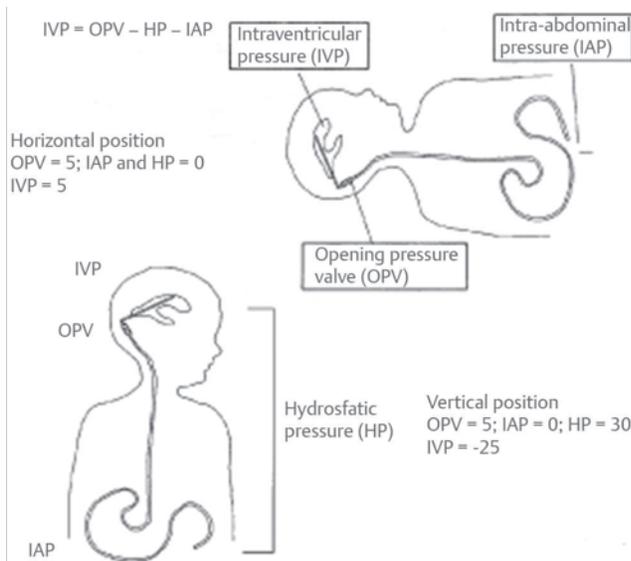


Fig. 10.5 Schematic diagram illustrating the siphoning effect in patients with shunts. Valve dynamics predominate in the supine position; hydrostatic effects predominate in the upright position. (From Drake JM, Iantosca MR. Management of pediatric hydrocephalus with shunts. In: McLone DG, ed. Pediatric Neurosurgery: Surgery of the Developing Nervous System. Philadelphia, PA: W. B. Saunders; 2001:508.96 Republished with permission.)

Codman-Medos programmable valve (Codman & Shurtleff) over standard valves.³⁷ In a prospective study examining the Strata valve (Medtronic Neurosurgical), 315 patients undergoing first shunt insertion ($n=201$) or shunt revision ($n=114$) received the valve. One-year shunt survival after first insertion was 68% and after shunt revision was 71%. These shunt survival data are similar to those published for other valves. Valve adjustments resulted in complete resolution of symptoms in 26% of the patients and an improvement in the symptoms of 37% of the patients. When symptoms improved or resolved, they did so within 24 hours in 89% of the adjustments that were made.³⁸ Although a clear advantage to adjustability has not yet been demonstrated in terms of shunt survival, many surgeons find this feature desirable in an attempt to relieve symptoms, maintain large ventricles, or deal with small fluid collections (► Fig. 10.6). The ability to adjust the valve pressure non-invasively, and thus potentially minimize subsequent operative manipulations of the shunt system, may warrant the increased expense and complexity of the programmable system.^{28,33,35,37}

10.4.3 Reservoir

A reservoir is very commonly used; it may be incorporated as part of the valve or added separately. It is usually placed near the valve or at the bur hole. It is useful for access to the CSF for

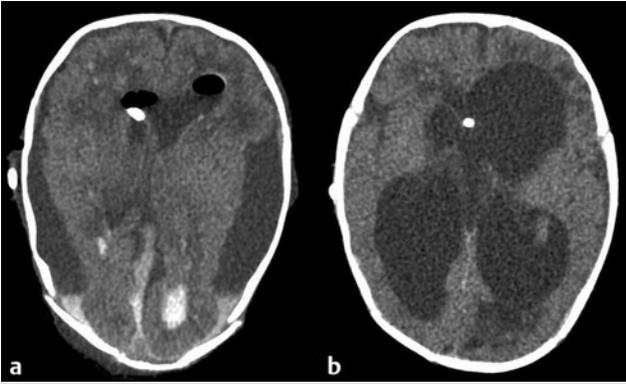


Fig. 10.6 (a) Subdural collections caused by overdrainage (b) can often be managed successfully by percutaneously increasing the valve pressure of a programmable valve until the subdural collections have resolved.

diagnosis of infection and occasionally for removal (or attempted removal) of CSF in emergent situations.

10.4.4 Peritoneal Catheter

Peritoneal catheters are also made of Silastic and impregnated with barium to make them radiopaque. The length is suitable for adult insertion, but the catheter can be shortened for use in children if necessary. In most cases, a full-term baby can accept nearly the full length, so elective lengthening is unlikely to be necessary. The catheters have an open distal end, and some have distal ports on the side. Peritoneal catheters are also available with a closed distal end and slits in the side of the tubing (distal-slit valves), which function in a differential-pressure fashion. In a review of 1,719 patients from Toronto and Paris, Sainte-Rose et al found that distal slit valves had a significantly higher failure rate than proximal non-slit valves.²⁵

10.4.5 Antibiotic-Impregnated Shunt Systems

Antibiotic-impregnated shunt (AIS) systems are designed to reduce bacterial colonization and the risk for infection. An AIS system was evaluated in a prospective, randomized clinical trial to determine whether it reduced the incidence of shunt infections compared with standard shunts. After a median follow-up of 9 months, 10 of 60 patients in the control group and 3 of 50 in the AIS group developed infections ($p=0.08$).³⁹ Parker et al published a systematic literature review with 12 studies comparing AIS and non-AIS systems.⁴⁰ Across these studies, 5,613 patients were identified with reported shunt procedures: 2,664 patients who received AIS systems and 2,949 patients who did not. The rate of shunt infection in pooled AIS patients was 3.3%, whereas the non-AIS patients had a rate of 7.2% (odds ratio [OR], 0.439; $p<0.0001$). These data favor the use of AIS systems; however, large randomized, prospective studies are needed to truly ascertain the absolute risk reduction obtained by using AIS systems.

10.4.6 Choosing the Appropriate Equipment

The amount of evidence that is available for choosing shunt equipment is limited. Probably the best advice is for a surgeon to become familiar with one system and use it consistently. Our preference is to use a straight ventricular catheter with a snap-on reservoir. A ventricular catheter integrated into the valve is not used, so that blood and debris can be drained away before the ventricular catheter is hooked up to the valve. An open-ended peritoneal catheter may or may not be integrated with the valve. A reservoir may be used as part of the valve system for access to CSF.

The choice of a valve has commonly been an area of great interest and controversy. A multicenter trial has compared a standard differential-pressure valve, a siphon-resisting valve (Delta valve; Medtronic Neurosurgical), and a flow-regulating valve (Orbis Sigma valve; Cordis Corporation) for children with newly diagnosed hydrocephalus.⁵ No significant difference was found in the time to first shunt failure among the three systems (► Fig. 10.7). Furthermore, as previously mentioned, clinical studies have not demonstrated a significant survival benefit for the adjustable valves (► Fig. 10.8 and ► Fig. 10.9) compared with standard valves.³⁷

10.5 Surgical Technique

10.5.1 Positioning

In the operating room, the patient is positioned under general anesthesia with the head rotated to the side opposite the proposed shunt. The neck should be extended with a bolster under the neck and shoulder so that there is almost a straight line between the scalp and abdominal incisions (► Fig. 10.10). Several studies have shown that prophylactic antibiotics covering skin organisms are effective⁴¹; therefore, they are strongly recommended.

10.5.2 Ventricular Catheter Placement Head Entry Site

The ventricular catheter may be inserted through a posterior parietal or a coronal bur hole. The relative merits of the two have been debated in the past. Data from a nonrandomized study with 10-year follow-up suggested better shunt function after coronal placement.⁴² In a randomized trial comparing these two entry sites,⁴³ 59% of the shunts inserted through an anterior bur hole continued to function at 14-month follow-up compared with 70% of shunts inserted through a posterior bur hole. This difference was not statistically significant, however, and the authors concluded that anterior placement did not offer any advantage over posterior placement. Anterior placement has been supported by some surgeons as the preferable method when endoscopic insertion is being performed. An anterior approach may allow better visualization of the foramen of Monro and catheter placement through an intraluminal endoscope. Its disadvantage is that it usually requires an additional skin incision behind the ear because it is difficult to make a direct

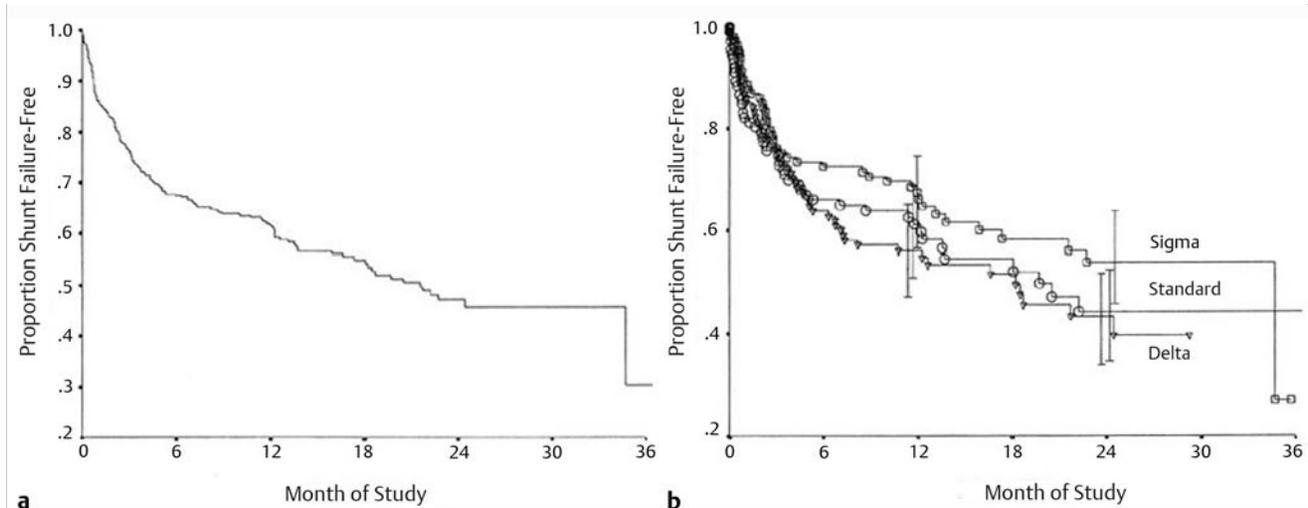


Fig. 10.7 (a) Overall results of the Shunt Design Trial. At 1 year, 40% of the patients had shunt failure. (b) Results of the Shunt Design Trial by valve. At 1 and 2 years there was no significant difference between valves. (From Drake, JM, Kestle JR, Milner R., et al. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery* 1998;43(2):2965. Republished with permission.)

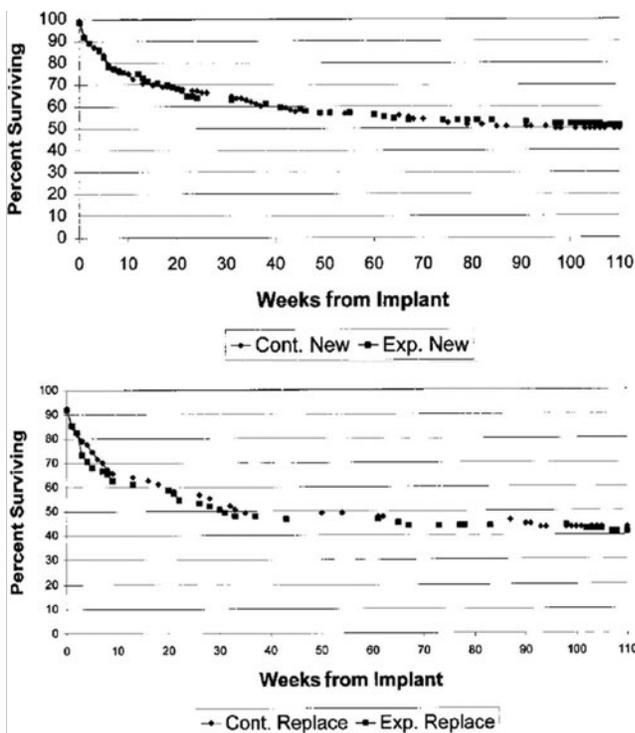


Fig. 10.8 Results of the programmable valve trial. Percentage of first shunt systems with no surgical intervention as a function of time from implantation in the experimental (Codman-Hakim programmable valve; Codman & Shurtleff) and control groups (conventional valve system). (a) Patients with no prior history of shunt placement. (b) Patients with a history of one or more previous shunts before study entry. Differences between the curves were not statistically significant ($p > 0.05$). (From Pollack I, Albright L, Adelson PD, et al. A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. *Neurosurgery* 1999;45(6):1402. Republished with permission.)

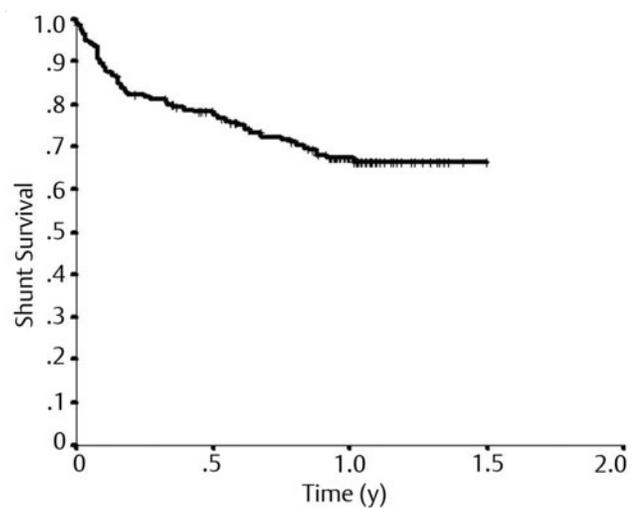


Fig. 10.9 Results of the Medtronic Strata (Medtronic Neurosurgical) valve trial. Kaplan-Meier curve demonstrating first-time shunt survival versus time. There was no significant increase in survival when this valve was compared with other valves from the Shunt Design Trial.³⁸

subcutaneous tract from the coronal incision to the site of the distal catheter.

Traditionally, the hair in the area of the cranial incision has been shaved or clipped. Shaveless shunt surgery has been reported, however, in which little or no hair is cut. The hair is washed, prepared, and left in the operative field. The experience is small, but infection has not been a significant problem.⁴⁴ The scalp incision should be placed such that the shunt hardware does not lie directly underneath it, particularly in younger patients with thin scalps. This helps to reduce the risk for erosion of the shunt through the incision. If a linear incision is desirable, it should be of sufficient length



Fig. 10.10 Optimal positioning of a patient for ventriculoperitoneal shunting includes a bolster under the ipsilateral neck and shoulder to make the subcutaneous pass from the valve to the peritoneum as flat as possible.

that the tissue can be retracted and the bur hole made medial or lateral to the incision. A curvilinear incision is another possible option.

When the opening in the dura is being made, care should be taken to make the opening just large enough to allow passage of the ventricular catheter. This will decrease the chance of CSF leak around the tubing. One method to create a small dural opening is to place a small brain needle against the dura and apply low-intensity monopolar coagulation to the needle.

Location of the Tip

To minimize the chances of proximal obstruction, the ventricular catheter tip should be placed away from the choroid plexus. Most surgeons choose the frontal horn, but based on their review, Sainte-Rose et al noted that the likelihood of ventricular catheter obstruction is lower when the catheter is placed posteriorly in the atrium of the ventricle via an occipital route.²⁵

In a randomized trial, Steinbok and colleagues compared ipsilateral and contralateral placement of the ventricular catheter in the ventricular system.⁴⁵ When the surgeon's intention was to place the catheter in the contralateral ventricle, 29% of patients developed ventricular asymmetry, whereas 48% of patients with ipsilateral placement developed asymmetry. When the analysis was based on the final location of the catheter (despite the surgeon's intentions), asymmetry was seen in 23% of the contralateral catheters and 54% of the ipsilateral catheters. There was no difference, however, in the shunt revision rate in the two groups.

In ESIT, there was no difference in shunt survival with or without endoscopic insertion.⁶ When the results were analyzed based on the final position of the catheter tip on postoperative imaging, it appeared that a location away from the choroid plexus was important in maintaining shunt function. Unfortunately, it did not appear that this was accomplished with the endoscope (► Fig. 10.11).

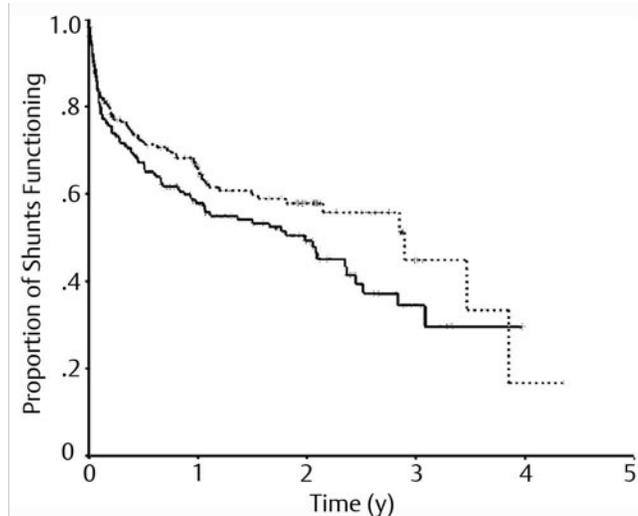


Fig. 10.11 Results of the endoscopic shunt insertion trial. Kaplan-Meier curves showing the shunt failure rates in the group of patients treated with endoscopy (solid line) and those treated without endoscopy (dotted line); $p = 0.09$. (From Kestle JRW, Drake JM, Cochrane D, et al. Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: a multicenter randomized trial. *J Neurosurg* 2003;98(2):287. Republished with permission.)

Loculate Hydrocephalus

Loculate hydrocephalus occurs when the ventricular system becomes obstructed by septa or cysts that develop congenitally or after hemorrhage, infection, or surgical trauma. This relatively uncommon entity is particularly difficult to deal with, as there can be numerous septa within the ventricular system that inhibit the drainage of CSF. Affected children sometimes end up with multiple intracranial catheters and/or multiple shunt systems. Complex shunt systems (incorporating three-way connectors or consisting of multiple linear shunt systems) have been shown to have a much higher failure rate than simple, linear shunts.⁴⁶

With the currently available endoscopic equipment, it is often advantageous to attempt fenestration of the septa or the septum pellucidum to allow communication between the locular compartments. Endoscopic fenestration can help reduce the rate of shunt revision, simplify existing shunt systems, and, in some cases, even avoid placement of shunts. When the experience with septal fenestration at Primary Children's Medical Center was retrospectively reviewed, 43 septostomies were performed in 32 patients over an 8-year period.⁴⁷ At a mean follow-up of 31 months, 81% of children had relief of their isolated lateral ventricle, with no septostomies failing after 6 months postoperatively. A prior history of multiple shunt procedures was highly predictive of initial septostomy failure, however, increasing this risk by 4.5. In some cases, successful endoscopic fenestration may require multiple fenestration procedures.

Before endoscopic fenestration is undertaken in multiloculate hydrocephalus, optimal radiographic imaging is essential to define anatomical and functional relationships between the cysts and the ventricular system. MR imaging provides the necessary

anatomical detail, but a CT dye study remains the best preoperative imaging study to verify lack of communication with the ventricular system and delineate to CSF compartments.

10.5.3 Adjuncts to Placement

Ultrasound

In a child with an open fontanel, ultrasound provides an excellent means by which to visualize the ventricular system and to observe the ventricular catheter as it is being inserted. A small amount of movement of the catheter is sometimes helpful; when this is done, the surgeon can usually identify the position of the catheter with respect to the ventricular system. There is some inconvenience in having to bring the ultrasound system into the operating room to perform the imaging; however, with practice it does not add much time to the procedure.

Endoscopy

Endoscopes are now available that fit into the lumen of the ventricular catheter. These allow visualization of the ventricular system as the catheter is being inserted. The goal when such equipment is used is to place the catheter away from the choroid plexus, which is thought to decrease the incidence of obstruction. Contrary to the results of several uncontrolled, retrospective case series,^{48,49} the multicenter, randomized, controlled ESIT demonstrated that, compared with standard placement, endoscopic placement of the ventricular catheter does not reduce the incidence of shunt failure in children undergoing initial VP shunt insertions (► Fig. 10.11).⁶ It is important to remember, however, that this trial did not evaluate the utility of the endoscope in shunt revisions. At Primary Children's Medical Center, we continue to use the endoscope frequently with shunt revisions because we believe the endoscope can be very helpful in situations of complex ventricular anatomy to confirm catheter placement within the ventricular system.

During placement of an endoscope, care should be taken not to change the angle of trajectory of the scope after it goes through the mantle of brain tissue. If this is done to get the catheter tip in a desired position, the catheter will probably move when the endoscope is removed and the deformed cerebral mantle will return to its baseline position.

10.5.4 Distal Catheter Placement

Peritoneum

The peritoneum is the preferred location of the distal catheter and the most commonly used. The rationale for this preference is that it is technically easy to gain access to the peritoneal cavity, and the peritoneum is extremely effective in absorbing CSF. It may be accessed via an open, small laparotomy and opened for catheter placement. A purse-string suture is placed around the catheter as it enters the peritoneum. Alternatively, an abdominal trocar through a paramedian incision can be used for peritoneal placement. We prefer to use a trocar because it is much faster, requires a small incision, and induces fewer adhesions at the site of entry. The disadvantages include a slightly higher risk for preperitoneal placement and vascular or visceral injury.⁵⁰ A trocar was used in 169 (23%) of 764 cases surveyed

by Di Rocco et al; abdominal complications were rare with either method.⁴⁵ As previously mentioned, the full length of an adult peritoneal catheter can usually be inserted in the full-term baby to allow for growth and to avoid a lengthening procedure.

Patients with multiple previous abdominal surgeries or morbid obesity present a unique challenge when the distal catheter is inserted into the peritoneum. At our institution, we consult general surgeons for laparoscopically assisted peritoneal shunt insertion in such patients. Laparoscopic insertion is a safe and effective way of placing the catheter into the peritoneum under direct visualization, with minimal risk for damage to the abdominal viscera. Additionally, placement of the distal catheter into the preperitoneal space in morbidly obese patients can be avoided with this technique.⁵¹

Alternate Distal Sites

It is very unusual that the peritoneum cannot be used for distal shunt insertion. Children with multiple abdominal operations, active abdominal infection (including necrotizing enterocolitis in preterm infants), or chronically elevated intra-abdominal pressure may require extraperitoneal shunt insertion. Choosing among the alternative sites depends on the clinical situation. In general, the second choice is usually the heart or the pleural space. In patients who have had multiple central venous catheters placed previously, it is often helpful to obtain an ultrasound preoperatively to confirm the patency of the venous system and to help determine which vein to use for access to the heart. The pleural space should be avoided in young children and children with lung disease. The gallbladder is a site that is used less frequently.⁵² A transdiaphragmatic insertion of a shunt into the subphrenic space has been reported.⁵³

Atrium

The technique of atrial insertion has been well described.⁵⁴ Access to the venous system can be achieved through an open or a percutaneous approach. Intraoperative fluoroscopy is used to position the distal catheter around the T6 level. A shunt system that incorporates a one-way valve must be used to prevent backflow of venous blood into the intracranial ventricular system.

With the high incidence of long-term complications, distal shunt insertion into the atrium should be considered a temporary alternative; every attempt should be made to remove the catheter from the venous system and replace it in the peritoneum or in the pleural space as the child grows. In one large series, two-thirds of revisions in 120 patients over an average follow-up of 11 years were performed to lengthen the catheter, whereas 8% of revisions were performed for distal obstruction.⁵⁵

Pleural Cavity

It has been asserted that pleural shunting is poorly tolerated in young children because of a lack of absorptive pleural surface, but the literature contains conflicting information. In a series by Piatt, one-third of infants required treatment for pleural effusions, although the treatment consisted of intermittent thoracentesis rather than shunt revision.⁵⁶ Only 2 of 19 older

patients, however, developed effusions. Various authors have recommended pleural shunting in successively lower age groups, and temporary use has been recommended even in children younger than 12 months of age.⁵⁷

Perhaps a more important contraindication than age is coexisting pulmonary dysfunction. Kyphoscoliosis, present in many patients with myelomeningocele, is one common condition limiting ventilatory reserve. In Piatt's series, 2 of 6 patients with myelomeningocele had symptomatic effusions, compared with none of the 16 remaining patients.⁵⁶ Both Piatt and Jones et al supported the use of siphon-restricting devices to avoid overdrainage.^{56,58} Although the negative pleural pressure can theoretically cause siphoning, no study has shown a significant improvement in pleural shunt survival with siphon-resisting devices.

Case-control and other published studies have not shown a difference between shunt survival rates for peritoneal and pleural shunts.⁵⁶ A pleural shunt may be a good choice when logistics require shunt placement with the patient in the prone position.

The distal catheter is inserted into the pleural cavity with a trocar. A small incision is made over a rib in the anterior or posterior axillary line. The trocar can then be advanced directly over the top of the rib into the pleural space, and the distal catheter is passed through the trocar. Continuous irrigation should be used to minimize the risk for a pneumothorax, but even if it is used, a postoperative chest X-ray should be checked for a pneumothorax.

Gallbladder

West et al reported a series of 25 patients with ventricle-gallbladder shunts.⁵⁹ Shunts were functional in 14 (70%) of the 20 patients with long-term follow-up. There were three early shunt failures: two due to proximal obstruction and one due to gallbladder atony (treated with cholecystokinin). Reflux of bile into the ventricular system has been reported in association with one patient's death.⁶⁰

10.5.5 Postoperative Care

Postoperatively, children are usually placed with the head slightly elevated. Sainte-Rose et al recommended wrapping the head with light compression to the cranial wound to minimize the collection of CSF around the shunt in the early postoperative days.²⁵ We do not routinely wrap the head after shunt insertions or revisions, and we have not had significant problems with subgaleal collections. Most surgeons monitor patients for 24 to 48 hours after a first-time shunt insertion to ensure the anterior fontanel is down and the wounds are healing before discharge. We routinely order CT of the head and a shunt series before discharge to ensure shunt hardware continuity and to have immediate baseline images for future comparison. We do not routinely administer antibiotics postoperatively.

Recently published data by Pearce et al suggest that the use of CT in children significantly increases the risk for leukemia and brain tumors.⁶¹ The analysis shows that the radiation doses from 2 to 3 CTs of the head in patients younger than 15 years of age triple the risk for brain tumors, and that the

radiation doses from 5 to 10 CTs of the head triple the risk for leukemia. In the population of pediatric patients with hydrocephalus, CT of the head is performed routinely after shunt surgery, often in the emergency department setting in cases of suspected shunt malfunction. At our institution, we are developing protocols to reduce the amount of radiation patients receive, both by improving education in the emergency department in regard to which patients require CT of the head for hydrocephalus and by not routinely ordering CT of the head for patients who clinically improve after shunt revision surgery.

10.6 Shunt Failure

10.6.1 Epidemiology of Malfunction

Articles on shunt malfunction report a remarkably consistent failure rate of 30 to 40% within the first year. In 1994, Di Rocco et al published the results of a cooperative survey of ISPN members.⁴ Thirty-eight neurosurgical centers submitted data on 773 patients. Two hundred twenty patients (29%) required a shunt reoperation in the first year. Although a univariate analysis of risk factors for shunt failure was performed with data gathered over a vague time period, the findings were as follows: (1) of shunts inserted at emergency surgery, 34% failed, compared with 29% of shunts inserted electively; (2) failure rates were the same for surgeons and residents; (3) unconscious patients had a 40% failure rate, compared with a failure rate of 30% in those whose consciousness was not impaired; (4) distal shunt insertion by open laparotomy had a 32% failure rate, compared with a 24% failure rate when a trocar was used; (5) the infection rates were 6.7% for patients who received prophylactic antibiotics and 4.5% for patients who did not receive prophylactic antibiotics; and (6) the failure rate for shunts inserted in the first 6 months of life (35 to 47%) appeared to be substantially higher than that for children older than 6 months (14%).

In a detailed review of an extensive experience, Piatt and Carlson reported on 727 shunt operations over a 13-year period.⁴⁶ Among the 671 simple linear shunts, the failure rate was 32% at 1 year. Simple shunts had better survival than complex shunts. Age was a significant risk factor for failure, with children younger than 2 years at higher risk than older children. Another interesting finding was that revision of a shunt after a short interval (less than 6 months) resulted in a risk for failure higher than that of new shunts or shunts revised after a longer interval. The cause of the hydrocephalus, duration of the operation, time of day of the surgery, and presence or absence of epilepsy did not have a significant effect on the risk for shunt failure. The conclusion was that factors under the control of the surgeon seemed to influence shunt survival to a lesser degree than factors intrinsic to the patient.

In their review of 1,719 patients, Sainte-Rose and colleagues found a shunt failure rate of 30% in the first year (deaths and infections were excluded).²⁵ They emphasized that different types of failure occurred at different times. For example, shunt fracture or disconnection tended to occur late, as did the need for elective lengthening of a shortened catheter. As previously mentioned, when univariate analysis techniques were used, the findings suggested a lower failure

rate with a posterior tip position than with a frontal ventricular catheter tip position, and a decreased failure rate for proximal compared with distal slit valves.

10.6.2 Types of Failure

Obstruction

Obstruction to flow can occur at any point along the shunt system; however, it most commonly occurs at the ventricular catheter. Obstruction of the ventricular catheter is probably the most common mechanical complication of shunts, accounting for 63.2% of mechanical complications.⁴ When the type of shunt failure was examined over time, proximal obstructions and infections were more common early after insertion; distal obstructions and disconnections were more common in late failures.⁶²

Although overdrainage is often discussed separately from obstruction of the ventricular catheter, the two may be related. If the drainage of the ventricular system is slow enough to keep the ventricles distended a little bit, the chance of the ventricular catheter adhering to the wall or becoming embedded in the choroid plexus may be lower. This notion is supported by a review of the data from Sainte-Rose et al, in which the rate of mechanical complications was 44.3% in cases of slit ventricles, compared with rates of mechanical complication of 27.1% and 36.1% when the ventricles were normal or enlarged, respectively.²⁵

Obstruction of the valve is much less common and usually occurs very early after shunt insertion or proximal shunt revision. Presumably, valve obstruction is due to cellular debris or blood that gets into the ventricular catheter, passes into the valve, and obstructs the valve.

Disconnection and Migration

Although rare, it is possible for the components of a shunt system to disconnect or for the whole system to move distally so that the ventricular catheter slides out of the ventricular system. These complications tend to occur early after shunt surgery, and they are easily detected on plain radiographs.

Fracture

Fracturing of shunt tubing is almost always a late complication.⁶² It is usually observed in tubing that has been in place for a long time, has become calcified, and has subsequently cracked. Commonly, the patient's shunt will function for a while after the fracture because CSF will pass through the fibrous sheath that usually surrounds the shunt tubing. Eventually, though, CSF flow fails and the patient presents with shunt malfunction.⁶³ Shunt tubing fractures are usually discernible on plain radiographs (► Fig. 10.12a). Fractured tubing most commonly occurs in the neck.^{63,64} In one large series, fractures were observed in 60 of 2,065 shunt procedures (3%).⁶⁵

Overdrainage

Shunt overdrainage either may be seen as extra-axial fluid collections or may be classified as SVS.

Extra-axial Fluid Collections

With the collapse of the ventricular system, extra-axial fluid and/or blood can accumulate (► Fig. 10.12). This was observed in 12 of the 344 patients (3.4%) in the randomized SDT.⁵ Extra-axial fluid collections usually occur in an older child with large ventricles early after insertion of a new shunt. Management of these collections can be very difficult; two primary approaches have been used: (1) decreasing or stopping the overdrainage, usually by changing the shunt valve to one with more resistance or to one with a siphon-resisting device; (2) draining the extra-axial fluid. The second approach may be accomplished by creating a bur hole and placing a temporary drain or by inserting a subdural catheter and connecting it to the existing shunt system below the valve. This latter option results in drainage of the extra-axial fluid with little or no resistance. The intraventricular catheter still has the resistance of the valve, and therefore there is a relative pressure gradient from the ventricular system out to the extra-axial fluid space, which results in brain expansion as the extracerebral fluid drains. The best treatment for this type of overdrainage, however, is to avoid it, and caution should be exercised in placing a shunt in the older child with large ventricles.

We have occasionally used programmable valves in high-risk patients. We tend to begin with the valve pressure set toward the higher end (e.g., Codman-Medos at 150, Strata at 2.0) and then gradually reduce the valve pressure over many months. Furthermore, in children who develop extra-axial collections, we have temporarily raised the valve to the highest setting and seen these collections resolve on follow-up imaging studies (► Fig. 10.6).

Slit-Ventricle Syndrome

There are children in whom very small ventricles develop in a delayed fashion after shunt insertion, and some of them are labeled as having SVS. A consistent definition of the syndrome is lacking in the literature. Perhaps a more convenient term would be *symptomatic small ventricles*. Nevertheless, the term *slit ventricle syndrome* is in such common use in pediatric neurosurgery that it is unlikely to change.

Affected patients have usually had a shunt in place for at least several years, and their ventricles have become very small over time (► Fig. 10.12e). In addition, they have symptoms similar to those of shunt malfunction. Their most common complaint is headache. Typically, the symptoms are repetitive or cyclical in nature and consist of intermittent headaches, nausea or vomiting, and other signs consistent with elevated ICP. The symptoms are often related to posture; patients may report improvement after a period of recumbency.⁶⁶ An acute presentation is also possible, with lethargy and coma.^{67,68}

In a retrospective review at Primary Children's Medical Center, it was noted that slit ventricles occurred in 270 of 370 patients (64%).⁶⁶ Only 18 patients (6.5%), however, had symptoms severe enough to warrant surgical management. In the ISPN survey, excessive drainage was observed in fewer than 1% of all patients with newly implanted shunts.⁴ SVS was not observed in any of the 344 patients in SDT (follow-up, 1 to 3 years).⁵ An incidence of 1.8% was observed in a series of 120 patients with ventriculoatrial shunts.⁵⁵

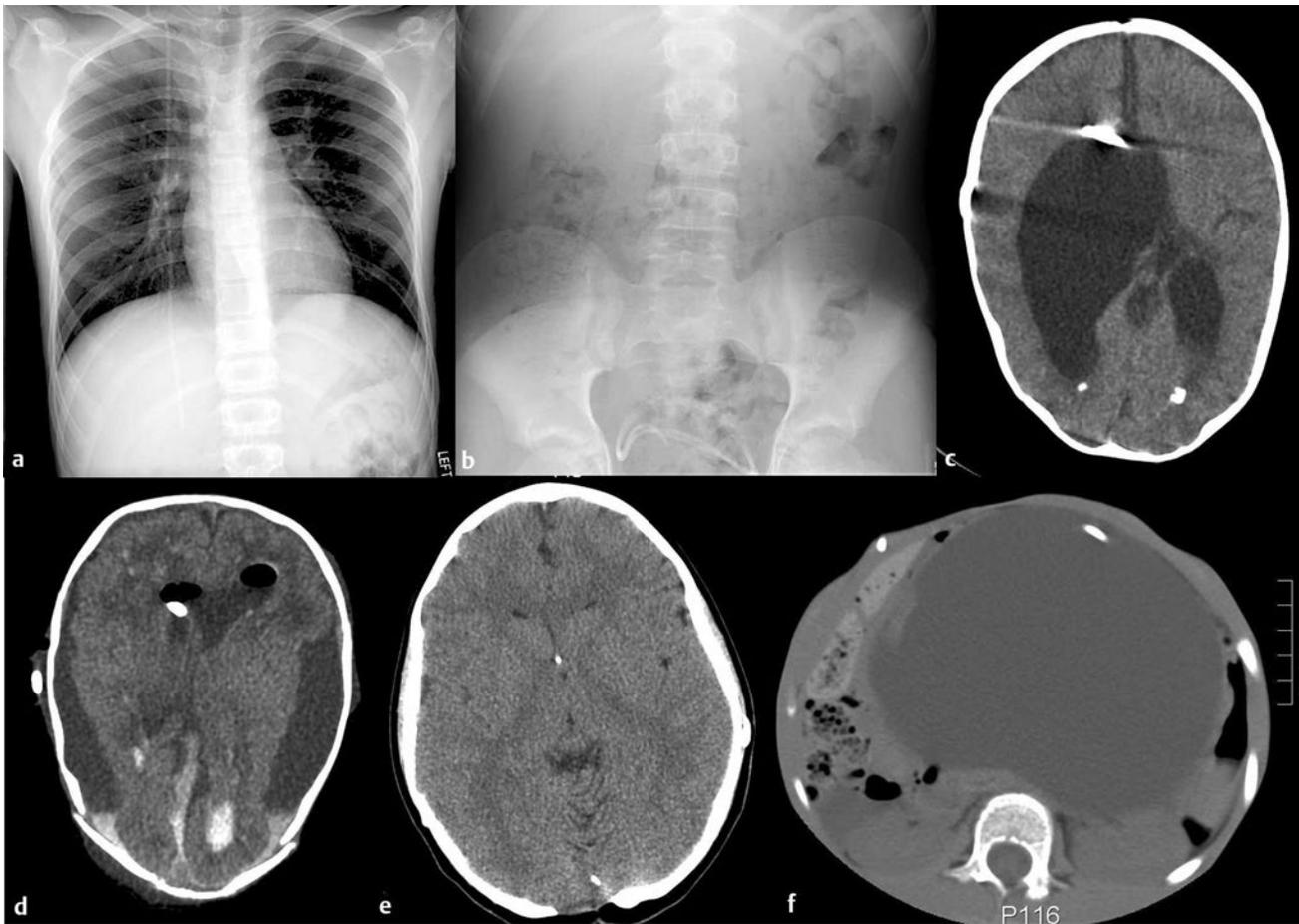


Fig. 10.12 Numerous types of shunt complications can occur, (a,b) including shunt fracture, (c) loculate CSF collections, (d) overdrenage leading to subdural collections or (e) slit ventricles, and (f) abdominal pseudocysts.

This syndrome presents quite late after shunt insertion, and its incidence may increase with longer follow-up. One study reported a mean time of 6.5 years to the development of a clinical picture.⁶⁹ When long-term follow-up (16 years) was obtained for 70 patients with shunts, Sgouros et al found a 10% incidence of SVS requiring surgery.⁷⁰

Pathophysiology

Although several pathophysiologic mechanisms have been proposed for SVS, none has received unequivocal scientific support. One hypothesis is that an implanted shunt system overdrenes CSF from the ventricular system because of the siphoning effect of the distal catheter. The siphoning is due either to the gravitational force of the column of fluid in the distal shunt tubing or, in the case of atrial or pleural shunts, to negative pressure environments at the distal tip of the shunt.

Overdrenage over the long term results in small ventricles and allows the brain to completely fill the intracranial space. As a result, the ability to compensate for transient changes in intracranial volume is impaired. In addition, the small ventricles cause intermittent ventricular catheter obstruction. This obstruction may be symptomatic without much (or any) change in ventricle size because of the brain's poor compensatory mechanisms. The underlying pathophysiology may also account

for the occasional incidence of sudden death in patients with shunts who have been found to have normal ventricles at autopsy.

Management

Although only a small percentage of children with shunts will develop SVS, the management is complex; they often account for a disproportionate number of shunt-related consultations and procedures. Conservative approaches that are appropriate in many cases include observation and medical therapy. In a review by Walker et al,⁶⁶ 13 (42%) of the 31 patients with the clinical diagnosis of SVS were managed successfully without surgical intervention. This approach is reasonable if a child's symptoms are infrequent and do not prevent participation in daily activities. Antimigraine therapy has appeared as an alternative first step in several articles and reviews.^{66,71,72} Whether the observation that some children with SVS improve on such therapy is a reflection of misdiagnosis or of efficacious therapy is not answerable at present. It has been argued that the child with SVS has such poor brain compliance that any factor that increases intracranial volume is highly likely to precipitate symptoms. In the case of antimigraine therapy, stabilization of the cerebral blood flow may minimize the intracranial volume changes and lead to symptomatic relief.

If conservative measures are not sufficient, several surgical approaches have been described.^{66,73} In some situations, ICP monitoring may be helpful. Low pressure during symptoms may respond to upgrading the existing valve, adding a siphon-resisting component, changing to a flow-control valve, or changing the setting of an adjustable valve. The management of patients with high pressure during symptoms is more problematic. Although cranial expansion and subtemporal decompression have been advocated in the past, shunt revision is now preferred. Revising the ventricular catheter in such patients can be difficult, and the surgeon runs the risk of not being successful at placing the new catheter. Several technical options have been suggested: (1) dilating the ventricular system under close observation and ICP monitoring, followed by reinsertion of the ventricular catheter; (2) using endoscopy, fluoroscopy, or stereotaxis during the revision; and (3) performing an endoscopic third ventriculostomy.^{74,75} Despite these maneuvers, managing such patients remains one of the most difficult and frustrating tasks in pediatric neurosurgery.

Loculation

Shunted ventricles are often asymmetric, with the lateral ventricle on the side of the shunt somewhat smaller than the one on the other side. Such asymmetry is usually mild, and the patient is asymptomatic. Occasionally, however, a shunt will drain only a portion of the ventricular system, leaving another area enlarged and causing mass effect (► Fig. 10.12c). Referred to as loculation, this scenario is very common in patients who have had ventriculitis or whose ventricles are loculate preoperatively. Although less common, it may be found in others as well. Isolation of a lateral ventricle has been described in a series of 8 patients without infection who presented 3 weeks to 7.5 years after shunt insertion. Two of them had IVH, and 6 patients were myelodysplastic. The proposed mechanism was overdrainage of the ipsilateral ventricle, resulting in functional obstruction of the foramen of Monro and a dilated contralateral ventricle.⁷⁶ When the experience at Primary Children's Medical Center was retrospectively reviewed, 43 septostomies were performed in 32 patients with an isolated lateral ventricle over an 8-year period. At a mean follow-up of 31 months, 81% of children had relief of their isolated lateral ventricle, with no septostomies failing at 6 months postoperatively. A prior history of multiple shunt procedures was highly predictive of initial septostomy failure, increasing this risk by 4.5.⁴⁷

Symptomatic children with an isolated fourth ventricle need to be treated. Sudden deterioration with cardiorespiratory arrest and death has been reported in one patient in a series of 10 who had an isolated fourth ventricle.⁷⁷ Of the 10 patients in the series, 9 presented with irritability and headaches, and 4 of 6 infants had opisthotonos. Imaging showed small or slitlike lateral ventricles; a large, rounded fourth ventricle; ventral displacement of the brainstem; and loss of the posterior fossa subarachnoid spaces. Treatment consisted of a fourth ventricle catheter that was added to the existing shunt, above the valve.

Infection

See Chapter 71 for a detailed discussion of shunt infections.

Mortality

Sainte-Rose et al observed a 1.05% mortality rate directly related to shunt failure in 1,719 patients over a 10-year period,²⁵ but a much higher mortality rate of 12.4% at 10 years was reported in a series of 907 patients.⁷⁸ The only risk factor for death was a history of shunt infection.

10.7 Follow-up of Patients after Shunt Insertion

After shunt insertion or revision, patients are usually reassessed within the first 2 or 3 months and then annually. The need for imaging studies at follow-up visits was investigated by Steinbok et al.⁷⁹ They retrospectively reviewed 86 children who had follow-up imaging studies. Of the 6 children whose first follow-up study was done beyond 3 months postoperatively, none had further change on subsequent imaging studies. The other 80 patients had studies before 3 months, and 39 (49%) of them had a further decrease in ventricle size on later images. Of the 14 patients who underwent imaging studies in the first 3 weeks after surgery, 10 (71%) showed further change on later studies. The authors concluded that a study done at 3 months postoperatively would be an adequate baseline for subsequent follow-up. Further information on this issue was obtained from SDT, in which all patients had a study between 2 and 4 months postoperatively; most patients also had a study at 1 and 2 years. The ventricle size was measured by a modified Evans ratio. Although the ventricle size at each time point had a wide range, it appeared that in most cases, there was a further decrease in the size of the ventricles at 1 year compared with 3 months. At 2 years, however, there was no further decrease in the size of ventricles.⁵

At Primary Children's Medical Center, we immediately obtain CT scans postoperatively and again at 3 and 12 months. Although the ventricles may continue to get smaller, the immediate and 3-month scans are still worthwhile because shunt failure is so common in the first year. If the shunt is still functioning at the end of the year, a 12-month image will provide a better baseline for long-term follow-up.

The other consideration is the type of follow-up study. In general, CT is used, and babies who start out with ultrasound are converted to CT when their fontanel closes.

10.8 Shunt Revision

VP shunt revision is probably the most common operation done by pediatric neurosurgeons. At the time of shunt revision, preoperative preparation and positioning should allow access to the whole shunt system because it is often difficult to predict the location of the malfunction. It is also important for the surgeon to be aware of the shunt system that the patient has in place so that the appropriate replacement needs is facilitated. In addition, the surgeon needs to be familiar with the different flow characteristics of different shunt systems in order to interpret the shunt function intraoperatively.

At Primary Children's Medical Center, our preference is to begin by opening the cranial wound, separating the ventricu-

lar catheter above the valve, and assessing the spontaneous flow (or lack thereof) out of the ventricle. Distal runoff through the valve and peritoneal catheter is also assessed with manometry. Interpretation of the latter maneuver requires knowledge of the valve in place and its usual expected flow characteristics. If poor runoff is obtained, it is important to then remove the valve and test the peritoneal catheter by itself to detect blockage within the valve. For patients with good runoff but poor flow from the ventricular catheter, the first maneuver is to remove the old ventricular catheter. The ventricular catheter is commonly stuck, and its removal with a Bugbee wire (Olympus Global, Center Valley, PA) can be very effective.⁸⁰ The Bugbee wire should be passed into the ventricular catheter with care so that it is not advanced beyond the tip of the catheter into the brain. The coagulating and/or the cutting current may be used to free the adhesions within the ventricular catheter. The catheter is then gently withdrawn, and a new one is passed.

Endoscopes are now available that will fit down the ventricular catheter during shunt revision surgery. The goal in such cases is to place the new catheter in a position away from the site where the old catheter was stuck. As previously mentioned, although ESIT did not demonstrate improved shunt survival with first-time shunts, the endoscope may occasionally be helpful in situations of complex ventricular anatomy to confirm catheter placement within the ventricular system.

If a valve is being replaced, it is most commonly replaced with one having the same flow characteristics unless the preoperative decision was to change the valve characteristics. This is usually not the case for shunt obstruction but may be appropriate in suspected overdrainage.

When there is a distal blockage, the whole peritoneal catheter should be replaced from the valve down to the abdomen. Cutting across the peritoneal tubing at the abdominal scar and attaching a new piece of tubing at that point with a straight connector results in fixation of the shunt at this point and predisposes to subsequent disconnection or fracture.

The peritoneal catheter may be replaced by using the tunneler for shunt insertion, or it can be pulled through the same tract by using the old peritoneal catheter or a guidewire.

10.9 Complications

Acute complications from insertion of the proximal catheter include hemorrhage and neurologic injury. Intraparenchymal hemorrhage related to shunt surgery occurs in approximately 1% of cases and is more common if the old ventricular catheter is removed.⁵⁰ Hemiparesis is possible if the catheter traverses the internal capsule, but in most cases this deficit is transient.

Abdominal visceral or vascular injury can occur after placement of a peritoneal shunt. Perforation of viscera can occur either at the time of shunt insertion or later from erosion of the tubing through the visceral wall.^{50,81,82} Perforations of the stomach, small and large bowel, bladder, and uterus have been reported.⁸³ Delayed erosion of catheters through bowel walls are thought to be more common with catheters reinforced with springs.⁸⁴

Pseudocysts are loculate pockets filled with unabsorbed CSF (► Fig. 10.12f). The cyst wall is a peritoneal serous membrane

thickened by chronic inflammatory tissue rather than by formed mesothelial tissue; thus, it is a pseudocyst. A low-grade shunt infection with *Staphylococcus epidermidis* or *Propionibacterium acnes* has been identified as the causative factor in 30 to 100% of pseudocysts, with most series reporting a rate of at least 60%.^{85,86} In addition to infection, multiple previous abdominal operations and chronically elevated levels of CSF protein have been identified as risk factors for the formation of pseudocysts.⁵⁰ Pseudocysts usually occur in a delayed fashion, even up to years after the last shunt operation, and can cause abdominal pain, distention, vomiting, fever, or poor appetite. The vast majority of patients with pseudocysts do not show symptoms of shunt malfunction.^{85–87} Treatment of the pseudocyst requires removal of the peritoneal catheter, at which time fluid from the pseudocyst can be aspirated in a retrograde manner through the catheter and the CSF and tip cultured. The pseudocyst typically subsides after the peritoneal catheter is removed; a laparotomy is rarely required. Given the high incidence of infection, at Primary Children's Medical Center we prefer to start antibiotic therapy immediately and continue it until CSF cultures are negative for 5 days. At that point, we typically convert the peritoneal shunt to an atrial or pleural shunt.

With pleural shunts, pulmonary parenchymal injury, pneumothorax, and effusion are the most common complications.⁵⁰ Most of these complications can be managed with observation alone. If pleural effusions become large and symptomatic, serial thoracentesis or removal of the distal catheter may be necessary. Distal components of ventriculoatrial shunts can cause thrombosis around the tip, with or without pulmonary embolus. This complication has been reported in up to 40% of patients with atrial shunts.^{88,89}

Craniosynostosis is a rare complication of CSF shunting that occurs only in patients who had a shunt placed before 6 months of age. Surgery is warranted if the child is developing well and the alterations in the cranial vault are cosmetically significant or if there is evidence of raised ICP in the presence of a working shunt. In such cases, cranial vault reconstruction may be necessary.⁵⁰

10.10 Shunt Removal

One of the most common questions asked by parents whose child is having a shunt placed for the first time is whether the shunt can be removed later. Another relatively common scenario is that of an older patient who returns for follow-up, apparently clinically well, with a disconnected shunt seen on radiographic examination, which might suggest that removal of the shunt is possible.

Whittle et al studied 46 children with arrested hydrocephalus.¹⁰ Thirty of these children had had shunts placed previously but appeared to be shunt-independent at the time of the review. The diagnosis of shunt independence meant that (1) the shunt had been clipped or removed or (2) an isotope shunt study had confirmed shunt blockage and serial neuroradiographic studies had confirmed that the hydrocephalus was not progressing. All of these patients underwent ICP monitoring, and 24 (80%) of the 30 patients with apparent shunt independence demonstrated intermittent or persistent intracranial hypertension. ICP tracings were normal in 6 (20%) of the 30 patients. On the basis of the results of the ICP recordings, all 24

patients had their shunt re-established, but clinical follow-up was not reported.

True shunt independence in children who have had shunts in place is uncommon; thus, great caution should be exercised in concluding that a child's shunt does not need to be fixed. Long-term vigilance with a very low threshold for re-evaluation is warranted because late deterioration after a period of apparent compensation and/or shunt independence has been documented.⁹⁰

10.11 Late Outcome after Shunt Placement

Late outcome after shunt placement depends in part on the cause of the hydrocephalus. Sgouros et al reviewed 70 patients who had shunts inserted between 1974 and 1978 and were followed for a minimum of 16 years.⁷⁰ Patients who died before the age of 16 years or who had tumors or posttraumatic hydrocephalus were excluded. The average age at follow-up was 19.1 years; the average age at shunt insertion had been 5.1 months (all 2 years of age or younger). Of the 201 shunt-related operations, 33 (16%) were performed on the children after the age of 16 years (26 shunt malfunctions and 7 infections). Of the children with myelomeningocele, 35 (50%) attended regular schools and 28 (40%) were in special school settings for the physically handicapped; 7 (10%) had mental handicaps that prevented normal education. Patients with meningitis and IVH had the worst outcomes, with mental handicap rates of 30% and 40%, respectively. Two-thirds of all patients were socially independent but living with parents (age-related), 12 children (17%) were dependent, and the remaining patients were either independent or married. Of the whole population, 10 children (14%) were either unemployable or required specially structured work environments. In this study, there were two late deaths and four major complications related to shunt malfunction and infection.

10.12 Issues in the Older Child and Adult

As the population of children with shunts ages, some issues relevant to young adults have appeared in the literature. Rekaté recommended that children who have large ventricles avoid contact sports.⁹¹ In addition, he suggested that young adults who have experienced coma when their shunts malfunctioned establish an outside contact system to ensure their well-being if they are living alone. The literature on managing shunts during pregnancy has shown that the presence of a shunt is not a contraindication to pregnancy; labor and delivery should be allowed to progress naturally.^{92,93} Interventions should be based on obstetric indications. Symptoms of shunt malfunction are common in pregnancy, but they resolve with delivery. Shunt pumping usually provides symptomatic relief in the interim.

10.13 Editorial Comment

The authors describe the multitude of factors that should be considered in making the decision about whether to insert a

shunt, a decision that is probably of more importance than the insertion site or shunt type. Kestle, Drake, and others who have conducted randomized clinical trials have increased our knowledge about shunting significantly.^{5,6} Technologically, we need methods to place ventricular catheters in the desired positions and to noninvasively measure ICP in patients with shunts, as well as methods to assess shunts that do not siphon.

Pearls

- Repeated assessments over time may be necessary to demonstrate progressive hydrocephalus that requires a shunt. In difficult cases, ICP monitoring may be helpful.
- When choosing shunt equipment, the surgeon should become familiar with one system and use it consistently.
- After shunt insertion, baseline images should be obtained immediately postoperatively and at 3 and 12 months. The decision not to fix a child's disconnected shunt should be made with great caution.
- Although endoscopically assisted placement of ventricular catheters has not been shown to extend the longevity of first-time shunts, it can be very helpful in shunt revisions to confirm catheter placement in the ventricular system.
- Placing the ventricular catheter tip away from the choroid plexus may reduce the chance of proximal shunt obstruction.

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11 Neuroendoscopy

Alan Cohen and Timothy W. Vogel

The field of neuroendoscopy has undergone an evolution in the past several decades, with increased attention given to minimally invasive approaches to various intracranial and spinal pathologies. With improved instrumentation, neurodiagnostic imaging, and surgical experience, pediatric neurosurgeons are now aware of the benefits and limitations of neuroendoscopy. Accompanying the improvement in surgical techniques and equipment is an ever-expanding base of scientific literature to help define patient selection, determine surgical outcomes, and describe potential complications and their management. Recent publications utilizing neuroendoscopic procedures have grown exponentially in the last decade and continue to expand in their diverse central nervous system (CNS) applications. Neuroendoscopy has been transformed as a field and is now part of a pediatric neurosurgeon's armamentarium, with neuroendoscopy incorporated into cerebrospinal fluid (CSF) diversion, tumor resections, intracranial cyst fenestrations, skull base approaches, and spinal surgeries. There is also a growing role for endoscopically assisted microneurosurgery in these aforementioned surgeries.

This chapter focuses primarily on intracranial approaches with neuroendoscopy, and there is some mention of its use in spinal surgery. The current instruments frequently employed in endoscopic approaches are discussed, as well as the orienting anatomy that is identified throughout the neuroendoscopic procedures. The current applications of endoscopy are also described, along with surgical decision making regarding the limitations of endoscopy. Finally, potential complications arising during surgery and strategies for their management are discussed.

11.1 History

The roots of neuroendoscopy actually begin within the field of urology. Victor Darwin Lespinasse, a urologist in Chicago, utilized a rigid cystoscope to fulgurate the choroid plexus in two infants with hydrocephalus. Walter Dandy, considered to be the father of neuroendoscopy, began utilizing this technique to extirpate the choroid plexus in cases of congenital hydrocephalus.¹ During his procedures, Dandy initially used a small nasal speculum to gain access to the posterior horns of the lateral ventricles and drain the CSF for access to the choroid plexus. Later, Dandy developed long-handled surgical instruments to accompany electrocautery in his endoscopic transventricular surgeries. Dandy developed an open form of third ventriculostomy for the diversion of CSF. The first endoscopic third ventriculostomy (ETV), however, was performed by W. Jason Mixer.² He developed the procedure in the cadaver of a child with hydrocephalus and translated his approach to patients. Around this time, in 1923, endoscopic photography was developed at the University of Pennsylvania by Fay and Grant, who captured the first endoscopic images of the choroid plexus.^{2,3}

These early innovations paved the way for more advanced optics and instrumentation, which were subsequently developed for cauterizing the choroid plexus in infants with hydro-

cephalus. Scarff at the Neurological Institute of New York at the Columbia University College of Physicians and Surgeons pioneered angled lenses⁴ to improve the field of view and utilized a monopolar electrode that could be advanced and retracted in a working channel of the endoscopic sheath.⁵ Scarff was able to irrigate the field and perform surgery at a fluid-filled interface, a technique that had been developed earlier by Putnam¹ to improve the primitive optics available at the time.⁶ Despite these adaptations, neuroendoscopy had a limited role in the treatment of hydrocephalus and was hindered by the considerable morbidity and mortality associated with these cases.⁷ With the introduction of the valved ventricular shunt in 1949 to treat hydrocephalus, the use of endoscopy declined.⁸

Unexpectedly, the same development that helped endoscopy fade from mainstream neurosurgery also helped it return to a critical role in pediatric neurosurgery.⁹ The complications of infections and shunt malfunctions associated with CSF shunt systems remain a persistent source of morbidity and mortality in children, and in an effort to reduce the shunt burden in children, neuroendoscopy¹⁰⁻¹³ has seen a resurgence in its use in the past two decades.⁷ In addition, instrumentation and optics have improved significantly and are now tailored to intracranial applications. With renewed interest, neurosurgeons employing neuroendoscopy¹⁴ are now exploring the boundaries of minimally invasive applications in various neurosurgical settings.

11.2 Instruments

11.2.1 Flexible and Rigid Endoscopes

The selection of endoscopes is critical for determining the types of surgical procedures that pediatric neurosurgeons undertake. The selection of available endoscopes is more diverse than the early cystoscopes, and innovation has been largely driven by technological improvements in digital imaging, optics, and minimally invasive surgical techniques. The types of endoscopes available can be generally classified as rigid and flexible, each having its advantages and disadvantages. Rigid endoscopes have traditionally had superior optics, relying on the segmental optics first pioneered by Harold Hopkins,^{15,16} an English physicist, and the optics are now coupled to a high-intensity light source, such as xenon. The rigid endoscope is introduced through a rigid sheath that can be equipped with several working channels to facilitate the introduction of microsurgical instrumentation as well as the ingress and egress of CSF and saline to flush debris and improve visualization. Adding these channels allows a fluid interface to be maintained throughout the surgery and ensures that the intracranial pressure (ICP) is kept at an atmospheric level, thereby preventing the accumulation of intracranial fluid and the resulting increase in ICP. Rigid endoscopes¹⁷ can also be outfitted with various angled lenses to widen the field of view around certain structures. Care must be taken when changing these lenses and steering through the ventricles and intracranial contents as orientation can be changed depending upon the lens angle selected.¹⁸

Additionally, rigid endoscopes and their sheaths are now available in a variety of sizes to accommodate neonatal pathologies.¹⁹

Rigid endoscopes, however, lack the maneuverability of their flexible counterparts. Flexible endoscopes can be used to peer around structures²⁰ with little movement at the cranial surface or translational movement through the cortex. Flexible endoscopes utilize fiberoptic technology to permit maneuverability, but this currently limits the amount of transmitted light. Flexible endoscopes²¹ require a different steering technique from rigid endoscopes to ensure that anatomical orientation²² is preserved throughout the procedure so as not to damage adjacent neural structures. Takanori Fukushima^{23,24} in Tokyo, Japan, is credited with pioneering the use of the flexible endoscope, primarily for biopsies of intraventricular lesions.¹⁵ Flexible endoscopes can now be used together with rigid endoscopes²⁵ in a scope-within-scope setup²⁶ in which the neurosurgeon can capitalize on the benefits of each scope.²⁷

11.2.2 Endoscope Holders; Digital and Three-Dimensional Imaging

A frequently overlooked aspect of neuroendoscopy is that a team,²⁸ in which an additional surgeon or a trained assistant is needed to manipulate the scope with an extra set of hands, often performs the surgery. It is advantageous to have one surgeon hold and manipulate the endoscope while another works with the instruments. To support the endoscopes and minimize translational movement through the exposed cortical surface, endoscopic holding arms have been invented that allow the operating surgeon to work alone (► Fig. 11.1). Pneumatically operated arms^{29,30} can be sterilely draped in the operative field and fixed in a locale that allows delicate microsurgical manipulation with a decreased risk for awkward movements or inadvertent changes in depth or direction throughout a procedure.³¹ In addition to rigid fixation of the endoscope, recent technology has made possible three-dimensional neuroendoscopy,² and improved digital imaging has become available and is moving two-dimensional images closer toward those seen during open microsurgery.³² Digital imaging ensures high-quality reproduction of the represented anatomy for the surgical team, and the

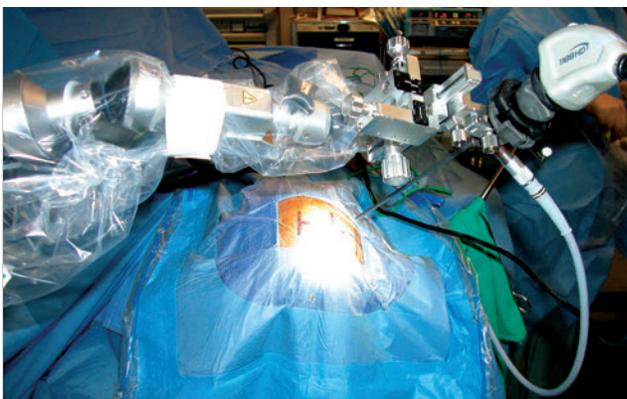


Fig. 11.1 Intraoperative picture of a pneumatic endoscope holder that has been sterilely draped and utilized to hold the neuroendoscope.

addition of three-dimensional imaging allows an improved appreciation of the relationships between neural structures. Three-dimensional imaging relies on two parallel cameras in the endoscope to display the digital images for three-dimensional reproduction.³¹ Regardless of the dimensionality used, digital images and movies allow better patient education regarding planned surgery and surgeon training in preparation for the encountered anatomy.

11.2.3 Surgical Instruments and Lasers

To accompany the scopes and digital imaging, surgeons have designed microinstruments³³ to facilitate dexterity during neuroendoscopic procedures.²⁶ These instruments are introduced through the working channels of the sheath and are separate from the irrigation ports for CSF and saline ingress and egress. The tools available to the neuroendoscopist continue to expand yearly, and they are designed for grasping, cutting, and sampling tissue.⁶ Rigid and flexible probes allow penetration through cyst walls,³⁴ whereas balloon catheters³⁵ allow the controlled dilation of openings made for ETVs,^{36,37} cyst fenestrations,^{38,39} septostomies,⁴⁰ and aqueductoplasties.^{20,21,41} Electrocautery with monopolar^{42,43} or bipolar current facilitates hemostasis and makes possible the manipulation of vascularized tissues, such as tumors, cyst walls, and choroid plexus.^{29,44} Multiple working channels on the sheath facilitate the use of two instruments concurrently to manipulate tissue.

Endoscopes may be outfitted with lasers⁴⁵ to permit cutting through tissues. The lasers most commonly utilized in neuroendoscopy are the neodymium-doped yttrium–aluminum–garnet (Nd:YAG) laser, the argon laser, and the potassium titanyl phosphate (KTP) laser.^{4,6,46} The Nd:YAG laser emits light with a wavelength of 1.064 μm , which is in the near-infrared spectrum, and the light is aimed with a visible helium–neon pilot beam. Nd:YAG lasers are used to cut or coagulate pigmented tissues, as laser absorption is preferential in these tissues.⁴⁷ KTP lasers⁴⁸ emit light with a wavelength of 0.532 μm , which is within the visible spectrum.⁴⁹ This laser can be used for dissecting because less thermal injury is produced.²

11.2.4 Stereotactic Endoscopy

Stereotactic navigation⁵⁰ and intraoperative real-time anatomical localization continue to improve neuroendoscopic surgeries. Preoperative high-resolution magnetic resonance (MR) imaging and computed tomography (CT) can be fused to allow pediatric neurosurgeons to plan surgical approaches and identify critical vascular structures that might otherwise limit their resections or exposures.⁵¹ During endoscopic surgery, there is always the potential for disorientation and potential injury to uninvolved anatomical structures. Multiloculate hydrocephalus^{52,53} requiring multiple cyst fenestrations for the communication of fluid spaces is a condition in which intracranial structures are difficult to differentiate from one another. Stereotactic localization^{54,55} helps orient the surgeon to the proper cyst wall and potential underlying structures. In addition, in transnasal surgeries,⁵⁶ preoperative CT of the skull base and maxillofacial region allow intraoperative midline orientation^{57,58} during attempts to identify the floor of the sella turcica and differentiate between anatomical variants with septate bone. Midline cranial

approaches, such as transcallosal^{59,60} surgery, may also benefit from stereotactic preoperative localization, in which venous lakes that communicate with the superior sagittal sinus are identified and intracranial entry can be planned away from these large cortex-draining venous structures.^{61,62} In addition, pediatric neurosurgeons, in an effort to reduce the amount of cortical injury in children, can plan approaches to minimize the length of the endoscopic trajectories used to reach a targeted region.

Intraoperative fluoroscopy^{30,63} and ultrasound may also be used if guidance systems are not available or become dysfunctional during surgery. In children with open fontanels, ultrasound^{53,64,65} over the anterior fontanel can be used to visualize the endoscope in relation to the underlying pathology.⁶⁶ One potential limitation of neuronavigation is brain shift and the collapse of fluid cysts or other fluid spaces once the endoscope has been introduced. Surgeons must be careful to correct for these changes during endoscopic procedures. Like all technology, stereotactic localization must be coupled with a working knowledge of anatomy to ensure that the information being displayed fits the anatomical endoscopic picture.

11.3 Endoscopic Anatomy

The following section focuses primarily on the intracranial anatomy encountered during transventricular approaches with the endoscope.^{20,67,68} There are key structures that need to be identified when the endoscope is introduced into the ventricles, and they serve as beacons throughout the case, reminding the surgeon of adjacent neural and vascular structures. Caution must be taken, however, as the normal anatomy may be obscured or distorted by the pathology of interest. If this occurs, neuronavigation with stereotactic localization may be utilized to verify the anatomy. In general, cranial endoscopy is safest if performed in the presence of ventriculomegaly, which allows the surgeon adequate visualization of the anatomical structures and room to maneuver the endoscope. If small ventricles are present, stereotactic localization may aid in cannulation of the ventricles.^{69,70} Before cannulation, proper scope orientation must be verified to ensure that the lens is not mistakenly inverted from a desired orientation.⁶³ This allows proper orientation throughout the case and prevents the inadvertent manipulation of tissue. In addition, when a transventricular approach to a lesion is used, a small needle with a stylet may be introduced into the cortex and ventricle to ensure that the planned trajectory and orientation traverse the ventricle.⁷¹ With the stylet⁷² removed and CSF appreciated, the endoscope can then be introduced along the trajectory of the needle as it is removed.

In general, the structures viewed with an endoscope look different from those visualized with a stereoscopic operating microscope.⁷³ The location of structures is relatively constant intracranially, but care must be taken for structures that lie outside the limited field of view while the endoscope is maneuvered. This becomes particularly important in depth perception, in which other signals, such as brightness, shadowing, and response to infusion of saline, will help the surgeon determine a structure and estimate its depth.²

The first structure that the endoscope encounters after penetrating the cortical surface and ventricular walls is often the floor of the lateral ventricle, which has a smooth, white ependymal surface. Here, the frondlike vascularized choroid plexus can be appreciated, lying in the choroidal fissure and leading anteriorly to the medial floor of the lateral ventricle. The choroid plexus then dives into the foramen of Monro and covers the roof the third ventricle posteriorly.^{67,74} The foramen of Monro serves as a landmark for endoscopists as it often guides surgeons to the proper location for an ETV or to the inspection of third ventricular lesions or the cerebral aqueduct (► Fig. 11.2). The foramen of Monro may be obscured, however, by intraventricular pathology, such as tumors, infections, or cysts. Identifying the choroid plexus overlying the thalamus in the choroidal fissure and leading to the foramen of Monro can help verify its location. An additional landmark that may be seen medially is the septum pellucidum, which may be patent or intact depending on the particular case. The head of the caudate nucleus may be seen lateral to the foramen of Monro. Neurovascular structures also serve as a roadmap intraventricularly, where the thalamostriate vein, coursing alongside the choroid plexus, joins the anterior septal vein at the foramen of Monro to form the internal cerebral vein.

Structures surrounding the foramen of Monro include the c-shaped fornices arching over the foramen. These fiber bundles contain efferent projections from the hippocampus and subiculum and define the anterior and medial borders of the foramen of Monro. The fibers terminate in the mammillary bodies on the floor of the third ventricle, where they appear as white prominences. Great care must be taken not to disturb the

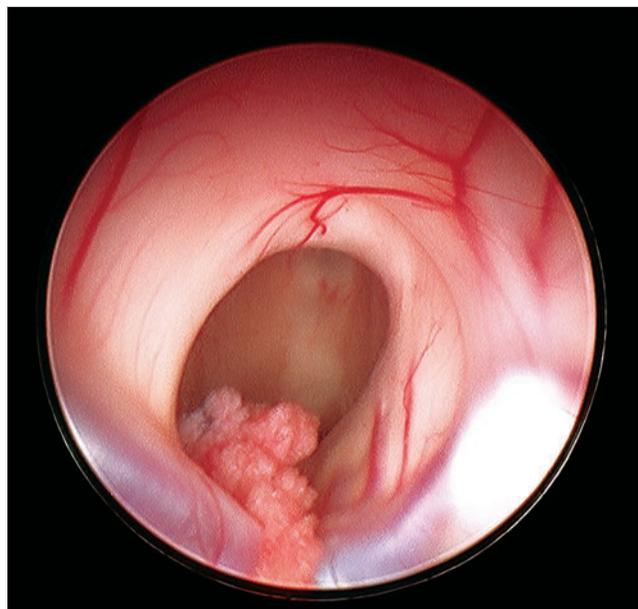


Fig. 11.2 Intraoperative anatomy seen during neuroendoscopy after the lateral ventricles have been entered. The foramen of Monro can be seen at the center of the image with the choroid plexus entering the third ventricle. The thalamostriate vein can be seen surrounding the posterior opening to the foramen of Monro, while the roof of the foramen is composed of fibers from the fornix. Damage to these fibers can be responsible for postoperative memory impairment.

fornices when the third ventricle is entered and the endoscope is manipulated.⁷⁵ As the third ventricle is entered, the anterior portion is appreciated, with the infundibular recess and anterior to it the optic recess. The tuber cinereum and the portion of the third ventricle between the mammillary bodies and the infundibular recess, is seen along with a vascular blush along the third ventricular floor. The tuber cinereum can be thinned out and stretched in the presence of hydrocephalus and may permit a view of the apex of the basilar artery in the interpeduncular cistern. The posterior third ventricle contains the aqueduct of Sylvius and posterior commissure, observation of which may be obstructed by a large massa intermedia. Visualization of these structures often requires changing the lens from a 0-degree scope to a 30-degree angled lens and turning a rigid endoscope around to look posteriorly.

11.4 Endoscopic Procedures

Intracranial endoscopic procedures can largely be classified as intraventricular and extraventricular applications. Conventional intracranial approaches utilizing the endoscope employ a bur hole or small craniotomy access through either one or several openings. The applications of neuroendoscopy continue to expand⁷⁶ in pediatric neurosurgery as investigators push the boundaries to define optimal patient populations.⁷⁷ Patient selection^{78–80} is clearly correlated with outcomes in a variety of neuroendoscopic procedures and ultimately determines their success in addressing pathologies.^{7,36} These approaches are largely driven by efforts to reduce manipulation of the normal cortex and minimize injury to surrounding neural⁵ and vascular structures with a minimally invasive approach.⁸¹ Endoscopy also seeks to reduce the postoperative length of stay, the length of surgery, and the morbidities and blood loss associated with open techniques.⁸² In some areas of pediatric neurosurgery, there continues to be debate⁸³ about the optimal approach and the role of neuroendoscopy.¹ In the following sections, a variety of neuroendoscopic procedures are discussed, along with the indications for surgical intervention and the subset of children who are potentially best suited for minimally invasive surgery.

The operating room setup for each endoscopic case depends on the approach being used. In general, however, the surgeons manipulating the endoscope and instruments should have the monitor placed in front of them so that their gaze is fixed on the screen and their access to surgical instruments is not obstructed (► Fig. 11.3). The surgeon holding the endoscope should have adequate room to avoid movement or disruption of the endoscope, with one hand firmly grasping the scope and the other on or near the cranium, ensuring that inadvertent plunging of the endoscope does not occur while instruments are introduced into the working channel.⁶⁶ When instruments are placed into the working channel, it is necessary to temporarily back out the endoscope a small distance to allow proper visualization of the instrument as it makes its way into the field of view. This prevents instruments from puncturing and damaging neural tissue outside the surgical field.⁶⁶ Additionally, the operating surgeons should verify the orientation of the lens if it is changed or added to the endoscope and should ensure that CSF has a proper egress from the brain by opening a working



Fig. 11.3 The endoscope and viewing screens are set up in a way that allows the surgeon to have maximal visualization of the ongoing operative procedure while also having access to the surgical instruments. The surgeon maintains fixation on the screen to ensure that no intracranial structures are damaged during endoscopic manipulation.

channel or appropriate port in the endoscope.⁸⁴ Finally, irrigation should be attached to the endoscope before the CNS is entered in order to avoid unnecessary twisting or manipulation of the endoscope. These small steps in endoscope setup help limit small-vessel or cortical hemorrhages throughout the endoscopic procedure.⁷⁵

11.4.1 Intraventricular Applications Third Ventriculostomy

The history of endoscopic surgery¹ to treat pathologies of the CNS is based upon the treatment of hydrocephalus with ETV.⁸⁵ Since its first use in 1922 by Dandy⁸⁶ as an open procedure, third ventriculostomy has undergone modification and is now incorporated into the realm of endoscopy as a standardly performed procedure.⁸⁷ The indications⁸⁸ for performing ETV normally include noncommunicating hydrocephalus with an open subarachnoid space for CSF uptake, although quantification of CSF absorption is difficult. Preoperative imaging⁶⁴ with MR imaging or CT reveals the presence of hydrocephalus and can help to determine if aqueductal stenosis or additional pathology is responsible for the obstruction in CSF flow.⁸⁹ MR imaging may reveal anatomical clues,⁹⁰ such as inferior bowing of the third ventricular floor, and can identify if the prepontine space⁹¹ is adequate for passing a blunt probe through the floor of the third ventricle. The location of the basilar artery can also be appreciated on sagittal MR imaging.⁹² Additionally, preoperative cine phase-contrast MR imaging gated to the cardiac cycle and performed in a midsagittal plane can qualitatively measure CSF velocity and flow and further identify the source and degree of CSF obstruction.^{93,94}

It was previously thought that in patients less than 1 year of age,¹⁶ myelomeningocele⁹⁵ (MMC)-related hydrocephalus, small ventricles, and infection of the CNS were contraindications to ETV.⁹⁶ However, studies⁹⁷ in each of these patient

populations have shown success⁹⁸ in reducing the proportion of patients who are shunt-dependent, suggesting that patient selection may not be as straightforward as one would hope.⁹⁹ Still, these more difficult scenarios must be taken into account when children and their parents are counseled as to the postoperative expectations with ETV.¹⁰⁰

ETV is performed under general anesthesia, and the patient is positioned supine with the head placed on a headrest elevated to about 30 degrees. The surgeon and assistant stand at the patient's head and look straight ahead at the digital monitor. If image guidance is being used, the authors prefer the head fixed in pin stabilization. The surgical site is prepared, and a small area in the midpupillary line just anterior to the coronal suture is marked about the coronal suture and make a bur hole or small craniotomy. The location of the bur hole may be adjusted by stereotactic localization in order to optimize the trajectory for making the third ventriculostomy and to observe any additional pathology that may be present.⁵¹ The authors prefer a more medial trajectory for ETV because it allows optimal visualization of the foramen of Monro and placement of the fenestration. The dura mater is opened, and the pia mater is coagulated and incised. The frontal horn of the lateral ventricle may be cannulated with a small needle or sheath of the endoscope to ensure that CSF is present.³³ CSF can then be collected for marker studies and histology if needed. The obturator in the sheath is removed, the endoscope is outfitted with a camera, and a light source is introduced. Irrigation tubing connected to the endoscope port allows lactated Ringer solution to enter the CNS, and an open channel allows CSF and fluid to exit.⁶⁶

The floor of the lateral ventricle and its ependymal surface are first appreciated along with the choroid plexus and foramen of Monro, which serve as landmarks for proceeding to the third ventricle (see ► Fig. 11.1).⁶⁷ The fornix is identified, and care is taken to avoid injuring this structure with instruments or the manipulated endoscope, because patients with forniceal damage may present with retrograde amnesia and verbal memory impairment postoperatively.⁴⁴ As the third ventricle is entered, the mammillary bodies are seen at the posterior aspect of the anterior floor along with the optic and infundibular recesses more anteriorly. The thin, translucent tuber cinereum contains only glial tissue and may be pulsatile from the underlying or adjacent basilar artery.¹⁰¹ A site of fenestration is chosen that is slightly more anterior^{14, 102} than halfway between the mammillary bodies and the infundibular recess. It is imperative to avoid vascular injury to the underlying basilar artery.

A 4F Fogarty balloon catheter with stylet or rigid probe is then passed down the working channel of the endoscope so that the end of the catheter can be seen in the operative field of view before it impacts any nearby structures on the floor of the third ventricle. The 4F balloon catheter is used to augment the opening (► Fig. 11.4a).^{82,103} The floor is then punctured at the desired site, with care taken not to plunge beyond the area of visualization. The opening is widened with balloon insufflation (► Fig. 11.4b). The endoscope can then be used to inspect the opening to identify the Lilliequist membrane,¹⁰⁴ an arachnoid plane containing the basilar artery complex and separating the posterior fossa cisterns from the suprasellar cisterns (► Fig. 11.4c).⁶⁸ This membrane must be opened to ensure

proper connection between the cisterns and the flow of CSF through the ETV. When the basilar artery complex and perforators are seen clearly, the pulsatile flow of CSF can often be observed through the opening in the third ventricular floor.¹⁰¹ Care must be taken around the opening of the floor of the third ventricle as excessive stretch may damage nearby basilar artery perforators or the hypothalamus, creating subarachnoid hemorrhage or autonomic disturbances, such as bradycardia.^{75,81,105} Laser perforation¹⁰⁶ has been utilized to open the floor of the third ventricle, but this may place adjacent vascular structures at increased risk for thermal injury during the procedure.⁴⁵ The authors advise against the use of laser perforation of the third ventricular floor.

The ventricles are inspected for any areas of hemorrhage and are copiously irrigated before removal of the endoscope. The patient is observed for 24 hours to ensure that flow through the ETV is adequate.^{101,107,108} Postoperative MR imaging¹⁰⁹ can determine the site and patency of the ETV, especially when it is combined with cine flow studies.⁹⁴ These images may be important to establish a new baseline for the affected child during subsequent evaluations. The ETV may not immediately affect ventricular size, and follow-up examination 6 weeks to 2 months later may reveal resolution of the ventriculomegaly.³⁷ Children may be followed intermittently¹¹⁰ in the postoperative period with MR imaging to ensure that ETV failure has not occurred. Long-term follow-up¹⁰⁰ may be required in certain cases as stomas in the floor of the third ventricle may lose patency, causing recurring symptoms and signs of elevated ICP.¹¹ In the setting of ETV failure, reinspection with an endoscope is warranted to determine the patency of the previous ETV and possible reopening of the closure. Occasionally, the stoma may be closed from gliosis¹¹¹ or infection, or plugged with cellular or proteinaceous debris, necessitating opening and exploration of the floor of the third ventricle. If the ETV is found to be patent, additional procedures, such as shunt insertion, may be required for poor CSF absorption in the subarachnoid space of the intracranial venous system.¹¹²

Outcomes¹¹³ of ETV vary depending on the definition of ETV success used by reports in the literature.¹¹⁴ ETV outcome studies describe primarily age and pathology as factors determining long-term outcome in children.^{14,103,115} ETV has also become a promoted therapeutic strategy for patients in underdeveloped countries^{82,116} to avoid the complications associated with shunts. The greatest success of ETV^{11,117} is seen in children with acquired, late-onset noncommunicating hydrocephalus resulting from tumor blockage¹¹⁸ of the aqueduct or fourth ventricle.¹¹⁹ The success rate for children meeting these criteria is as high as 80 to 90%.^{82,120-122} Lower success rates are reported in children less than 1 year of age^{110,117,123} or with a history that includes CNS infection, MMC, communicating hydrocephalus, the presence of a preoperative shunt system, or congenital aqueductal stenosis.^{14, 115,123} The presence of a shunt system¹²⁴ is not an absolute contraindication to attempting an ETV¹⁰⁸; ETV may allow the child to become shunt-independent. Also, approximately 50% of neonates with an MMC^{95,125} may respond to ETV, so that they are liberated from shunt placement in a disease that was once thought to be synonymous with shuntable hydrocephalus.¹²² ETV for children with an MMC^{81,95} may be complicated

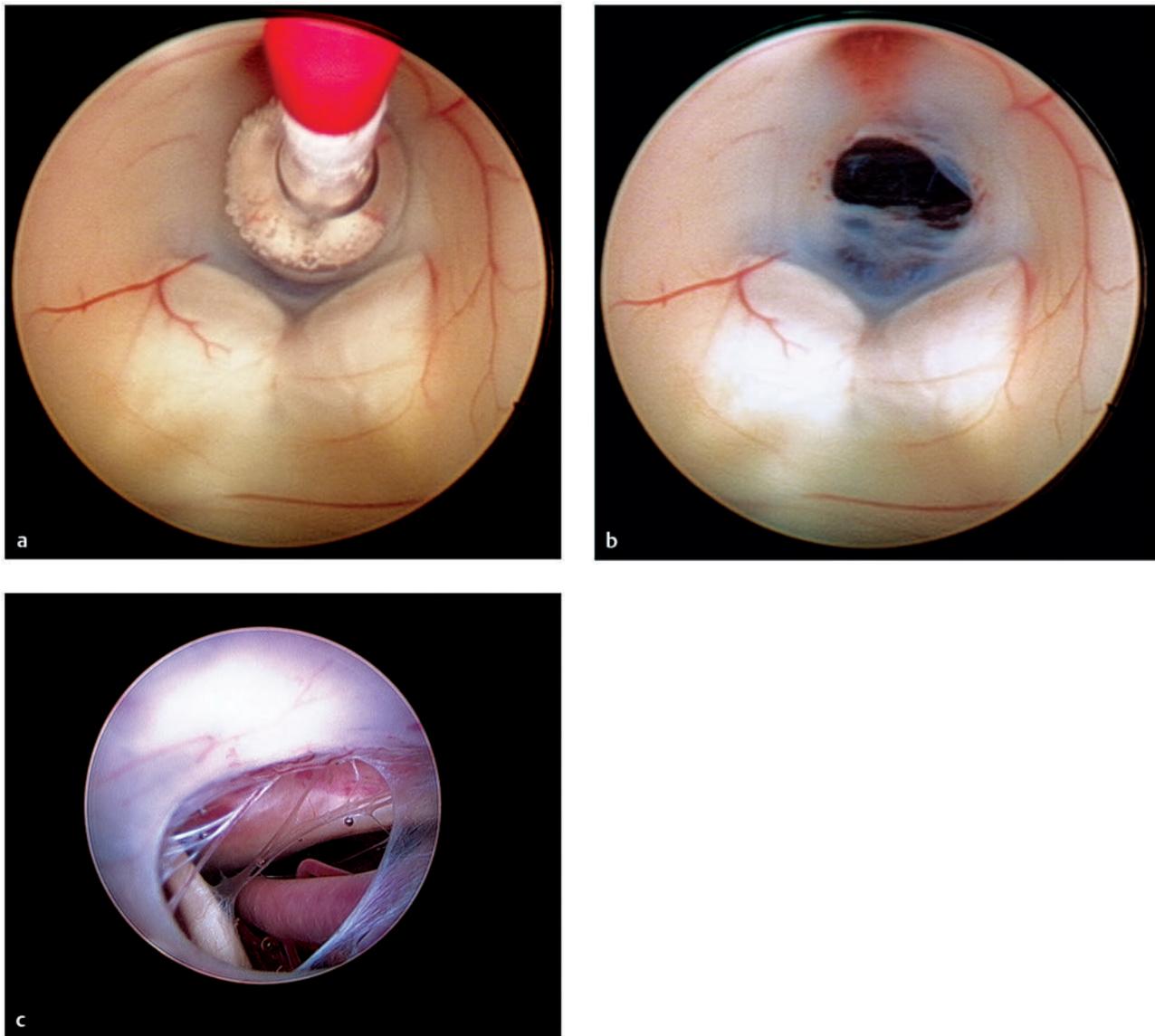


Fig. 11.4 Endoscopic third ventriculostomy. (a) A Fogarty balloon catheter has been introduced through the working channel of the neuroendoscope and is seen in the floor of the third ventricle. The opening for the ETV is made just superior to the paired mammillary bodies in the tuber cinereum of the floor of the third ventricle. The balloon catheter is dilated until the ETV opening is made. (b) The opening in the tuber cinereum in the floor of the third ventricle can be visualized and is superior to the paired mammillary bodies. The blush of the infundibulum can be seen superior to this opening. (c) An endoscopic view through the ETV opening; the basilar artery can be seen, along with the remnants of the Lilliequist membrane.

by the abnormal intraventricular anatomy that is frequently encountered, necessitating conversion to placement of a ventriculoperitoneal shunt system. Such anatomical limitations include abnormalities in the skull base limiting the prepontine space⁹¹ and abnormal ventricular anatomy. The long-term cost-effectiveness¹⁰ of ETV in comparison to shunts, however, is an area of considerable debate, and additional studies are warranted⁸³ to determine its use in various populations of children.¹⁰

Complications arising from ETV^{37,45,117,123} include hemorrhage¹²⁶ from damage to the basilar artery, infection, midbrain injury, third nerve palsy, hemiparesis, neuroendocrine deficits from damage to the hypothalamic nuclei, subdural hematoma,

fever unrelated to infection, and damage to the fornix resulting in memory impairment.^{12,81} Many complications¹²⁷ are transient in nature and resolve in the immediate postoperative period on follow-up examinations.^{37,78,79,93,97,108}

Multiloculate Hydrocephalus

Multiloculate hydrocephalus and isolated ventricles can result from any inflammatory¹²⁶ or infectious¹²⁸ process within the cerebral ventricles and can lead to trapped CSF spaces that complicate the clinical presentation and treatment of a child with hydrocephalus. Isolated ventricles may result from overdrainage of CSF in infants, leading to slit-ventricle syndrome and

isolation of a lateral ventricle from the rest of the ventricular system.¹²⁹ Equilibration of the ventricular system may not occur after shunt placement, and overdrainage of the ipsilateral ventricle may cause the contralateral ventricle to dilate. Similarly, if the aqueduct of Sylvius collapses, a dilated fourth ventricle may develop, compressing the adjacent brainstem. Postinflammatory hydrocephalus results from infection or hemorrhage within the CNS and can lead to scarring of the subarachnoid spaces, decreased CSF absorption, ependymal cyst formation, and obstruction of CSF flow.¹³⁰ With its narrow gauge, the aqueduct of Sylvius is particularly vulnerable to occlusion from inflammation. Gram-negative ventriculitis and perinatal intraventricular hemorrhage may result in subependymal cyst formation that may later exert mass effect on the surrounding ventricles, impeding and ultimately obstructing CSF egress.^{48,131}

Patients with numerous cysts are more complex cases than those with uniloculate cysts as these children may have undergone numerous shunt revision surgeries necessitating multiple catheter placements to control expanding cysts. The ultimate goals in treatment, however, are similar in both cases; the objective is to provide communication and CSF flow between all isolated compartments with the ventricular system. Shunt placement in these patients is fraught with challenges¹³² as collapse of the cyst around the shunt catheter or scarring at its tip may obstruct CSF flow.¹²⁹ Balancing CSF pressures to prevent collapse and maintain flow is also difficult to determine with a shunt and its valve, leaving only trial and error and multiple surgeries as the answer to this dynamic problem.

In order to treat children with multiloculate or uniloculate hydrocephalus more effectively, pediatric neurosurgeons are turning increasingly to the use of endoscopy to reduce the need for shunts or to decrease the overall shunt burden in these patients. Endoscopic cyst fenestration aims at making sufficiently large holes (> 1 cm) in each cyst wall and having the cysts communicate with either the native ventricular drainage systems, if they are present, or with a shunt catheter.¹³³ Cyst walls are also devascularized to help reduce the potential for closure of the stoma. The fenestrations of multiple compartments in the ventricular system are not, however, straightforward, and surgeons employ additional technology to improve fenestrations into known compartments, avoiding unnecessary manipulation of nearby neural structures. One technology that has been utilized to guide cyst fenestrations is stereotactic management, in which each cyst wall can be verified before marsupialization. Intraoperative MR imaging^{51,130,134} may also be used in conjunction with endoscopy to reduce the number of isolated cysts present in the CNS and to ensure maximal communication between the multiloculate locations. If the child has open fontanelles, intraoperative ultrasound may also be used to verify the collapse of cysts throughout the brain.¹⁵

Before surgical intervention, preoperative MRI may improve the anatomical localization of each cyst wall in relation to the ventricular landmarks.⁵¹ The surgeon can plan multiple trajectories to determine the entry point in order to optimize the number of cysts fenestrated and identify an area where these can be made to communicate with the native ventricular system or with a shunt catheter to be left in place. Entry points can also be selected to avoid eloquent cortex and neurovascular structures, which would otherwise limit the fenestration attempts. Surgical access also depends largely on the location of the cysts;

those located in the anterior or body of the lateral ventricle require a precoronal bur hole, whereas those in the temporal or occipital horns may require a bur hole in the occipital region.¹³³ After the optimal trajectory has been planned, the patient is placed under general anesthesia and prepared, and the planned incision is made. Using a combination of blunt probes, forceps, scissors, and electrocautery, the surgeon creates cyst fenestrations through the involved areas. Landmarks on the floor of the lateral ventricle are identified but may initially be obscured by cyst walls. Verifying location throughout the process with stereotaxis⁵³ is essential to avoid collateral injury to nearby vital structures. At the end of the procedure, the ventricles are inspected for evidence of communication and for lack of hemorrhage, and if needed, a shunt catheter or ventriculostomy catheter is placed.¹²⁹

Endoscopy has been shown to significantly lower the shunt revision rate in multiloculate hydrocephalus,¹³³ and postoperative imaging may confirm the fenestrations made. Children should be followed carefully during the first several months after surgery to ensure that closure of the stomas does not occur.¹²⁹ Long-term follow-up studies with MR imaging may also indicate increased growth of particular cysts and track the equilibration process. Patients with multiple cysts may be up to seven times¹³⁰ more likely to need a repeated endoscopic procedure than patients who underwent endoscopic fenestration before shunt placement. Repeated endoscopic procedures for multiloculate cysts are required in up to 33% of cases; however, complex shunt systems for these patients could be simplified in 75% of patients.¹³⁵ Endoscopy reduced the need for cystoperitoneal shunt revision from 2.9 revisions per year to 0.2 revisions per year.^{20,41}

Alternative treatment strategies exist for an isolated fourth ventricle²² an aqueductoplasty with or without the use of stent assistance aims to introduce normal CSF flow through the aqueduct of Sylvius. A short segment of aqueductal stenosis is preferable¹¹⁹ when an aqueductoplasty is performed, and the surgical approach may originate through an anterior bur hole with access through the third ventricle. Alternatively, a suboccipital approach²¹ through the cerebellomedullary cistern may be used to access the foramen of Magendie.¹¹⁹ Stents placed in the aqueduct consist of normal ventricular shunt tubing that may be connected to subcutaneous reservoirs or existing shunt systems. Stents can be deployed with rigid, flexible, or flexible-in-rigid²⁵ endoscope arrangements.²² Care must be taken to avoid injury to adjacent structures in the midbrain²⁰ and to avoid prolonged occlusion of the cerebral aqueduct because it may result in bradycardia or neurologic deficits.¹⁰⁰

Arachnoid Cysts

Arachnoid cysts account for 1% of intracranial lesions, and with improved neuroimaging techniques in children, their diagnosis has increased. Arachnoid cysts are thought to be congenital, and their etiology and pathogenesis are unclear.^{28,39,51,136} These intracranial lesions may result from a one-way CSF valve, osmotic gradients within the cyst, or increased fluid synthesis from the cyst wall. Fifty percent of arachnoid cysts are located in the middle fossa; 10% arise in the cerebral convexity, 10% in the midline posterior fossa, 10% in the suprasellar cistern,¹³⁷ 10% in the cerebellopontine angle, and

10% in the quadrigeminal cistern.¹³⁸ Children may present with headaches, ataxia, seizures, or hemiparesis,¹³⁹ depending upon the size and location of the cyst, and they are at increased risk for spontaneous or posttraumatic hemorrhage into the cyst or into the subdural space.^{140,141}

The management of arachnoid cysts is controversial, and surgeons familiar with a particular approach frequently advocate endoscopy or microsurgical approaches.^{38,139,140,142,143} A review of arachnoid cysts treated with endoscopic techniques revealed that clinical resolution of symptoms was achieved in 90% following fenestration, and a decrease in cyst size was seen in 75% of patients. Postoperative complications were found in 16% of cases,³⁸ with the most common middle fossa cysts having the

highest recurrence and complication rates as well as the lowest clinical response rate.^{39,138} After fenestration (► Fig. 11.5), children with arachnoid cysts should be followed over several years for delayed recurrences. Similar success rates have been reported for cystocisternostomy and ventriculocystostomy²⁸ as for ventriculocystocisternostomy, in which communication is made between the basal floor of the cyst wall and the underlying cisterns.¹⁴¹ Quadrigeminal cysts¹³⁶ may compress the aqueduct of Sylvius and are amenable to endoscopic treatment because they are adjacent to the third ventricle. Patients with these cysts frequently present with macrocephaly, headaches, and ataxia. Fenestration options include ventriculocystostomy and ventriculocystocisternostomy, and success rates

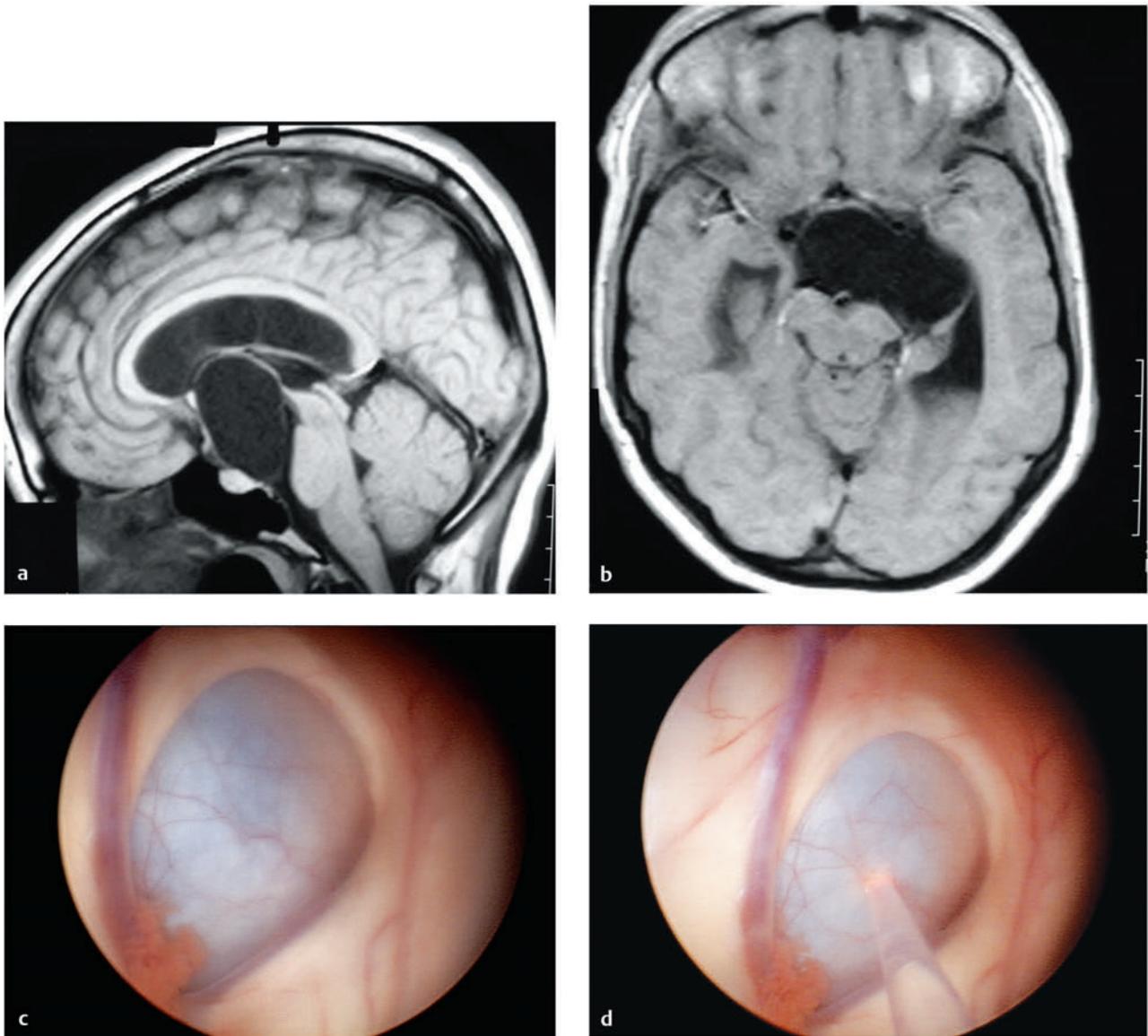


Fig. 11.5 Suprasellar arachnoid cyst. (a) Sagittal T1-weighted noncontrast magnetic resonance (MR) image of a large suprasellar arachnoid cyst with compression on the ventral pons. (b) Axial T1-weighted noncontrast MR image of the same suprasellar arachnoid cyst with compression on the cerebral peduncle. (c) Endoscopic view of the arachnoid cyst with obstruction of the foramen of Monro. The choroid plexus can be seen adjacent to the cyst along with the septal vein that runs along the left side of the image. (d) Endoscopic view of the arachnoid cyst with yttrium–aluminum–garnet (YAG) laser used to fenestrate the cyst wall.

range from 70 to 90%, depending upon the series and surgical methods utilized.¹³⁶

Shunting is also a therapeutic option, with cystoperitoneal shunt placement, but it may be associated with subdural hematoma formation from a rapid decrease in cyst size. Open surgery for cysts is frequently employed, and success rates vary from 54 to 96%. Open surgery is also associated with a 7 to 12% reoperation rate.²⁸ The advantage of using the endoscope in the treatment of arachnoid cysts is the minimally invasive approach, which avoids a larger craniotomy. Lower risk for hemorrhage and for altering the resorptive capacities of the subarachnoid space has been reported with the use of endoscopes. The success rate of neuroendoscopy in arachnoid cyst fenestration varies from 66 to 96% in the resolution of clinical symptoms and is 80% in reduction of cyst size.²⁸ One area in which endoscopic surgery has supplanted open microsurgical technique is in the treatment of pediatric suprasellar arachnoid cysts; success rates in the reduction of cyst size have improved while the comorbidities associated with an open procedure have been limited.¹³⁷ Failure rates for endoscopic cyst fenestration are similar to those of open microsurgical approaches, with rates ranging from 3 to 17%.³⁹ The optimal treatment for symptomatic and asymptomatic arachnoid cysts remains unclear, and it is hoped that future studies will continue to clarify the use of neuroendoscopy in children with these lesions.¹⁴⁴

Parasitic Cysts

Neurocysticercosis (NCC), resulting from infection with *Taenia solium*, is the most common parasitic infection in the CNS and can lead to hydrocephalus in approximately 30% of affected patients.¹⁴⁵ NCC is estimated to cause 50,000 deaths each year in Latin America, and parasitic cysts are often seen in the lateral and fourth ventricles in children, occluding the foramen of Monro or the cerebral aqueduct.²⁶ Noncommunicating hydrocephalus can result from the obstruction of CSF flow. Treatment for NCC infection includes antihelminthic medications such as albendazole, microsurgical removal of cysts, treatment with steroids and antiepileptic medication, ventriculoperitoneal shunting, and endoscopic retrieval of cysts.¹⁴⁶ Endoscopy is the favored treatment modality for patients with obstructive hydrocephalus, and various endoscope setups may be utilized to retrieve parasitic cysts in the fourth ventricle. Flexible endoscopes placed in rigid endoscopes utilize the advantages of each technology, with a flexible endoscope navigating the challenging anatomy of the fourth ventricle.²⁵ Aspiration devices in rigid scopes or flexible biopsy forceps to retrieve offending cysts are alternative setups in cases of NCC. Shunts have an estimated complication rate as high as 88%¹⁴⁶ in NCC, and the use of neuroendoscopy avoids these comorbidities. In addition, 84% of patients whose NCC is treated with endoscopy require only one surgery to address their hydrocephalus, thereby reducing the need for additional shunt procedures.¹⁴⁷

Intraventricular Tumors

Intraventricular tumors comprise an estimated 2% of all primary CNS tumors, and neuroendoscopy is increasingly used in biopsy for diagnosis and in resections. Intraventricular tumors in children include the following: astrocytoma, meningioma,

craniopharyngioma, ependymoma, giant cell tumor, choroid plexus papilloma or carcinoma, subependymoma, germ cell tumor, teratoma, lymphoma, primitive neuroectodermal tumor, and central neurocytoma.^{148–150} Endoscopes can be used in a variety of ways to address intraventricular tumors; biopsies can be performed alone or in concert with ETV CSF fluid diversion¹⁵¹ or tumors may be resected with the endoscope, and a variety of microinstruments have been developed to work within the ports of the scope.^{24,55,118,152}

The mainstay of neuroendoscopy in the treatment of intraventricular tumors is centered upon treating hydrocephalus, and this can be paired with biopsies¹⁵³ of the lesion. The alternative to endoscopic biopsies in children is the use of stereotactic biopsy.^{50,154} Large series of patients undergoing stereotactic biopsy report mortality rates of 1 to 4%, morbidity of 4%, and diagnostic accuracy of 91%.¹⁵⁴ Neuroendoscopy has lower mortality rates, variable morbidity rates ranging from 0 to 17%, and diagnostic accuracy ranging from 70 to 100%, depending upon the series.^{23,24,55,118,152,155} Rigid endoscopes are correlated with higher diagnostic rates than are flexible endoscopes.^{73,118,156} Endoscopic series of tumor biopsies may have higher morbidity rates because there is a larger opening affecting nearby neural structures, including the fornices, and because it is difficult to control the most common complications of CSF leakage and intraventricular hemorrhage. The advantage of endoscopy is direct visualization of the tumor in relation to other adjacent structures, allowing a full inspection of the anatomy before biopsy, whereas a stereotactic approach is essentially a blinded procedure guided by computer representations of the anatomy. Endoscopic biopsy has the added benefit of coupling tissue sampling with concurrent CSF diversion or tumor debulking.^{157,158} Recent studies on the administration of fluorescent dye to visualize tumors and improve the results of diagnostic biopsy are promising.¹⁵⁹

Frameless stereotactic systems can be combined with microsurgical and endoscope-assisted resections¹⁵³ of intraventricular lesions to improve localization and the amount of tumor resected.¹⁶⁰ Intraventricular tumors are frequently approached through an ipsilateral bur hole, with the tumor accessed through a dilated lateral ventricle.^{155,161} With technical innovations in surgical instrumentation, devices can now aspirate and evacuate tumor. Oscillating microdebriders,¹⁶² ultrasonic aspirators, and variable-aspiration resection devices can be deployed through the working channel to improve tumor manipulation and extirpation. The improvements in these devices continue to advance the surgeon's ability to remove tumors through the minimally invasive approach. Alternatively, endoscopy following the microsurgical resection of an intraventricular tumor allows a surgeon to inspect the resection bed for residual tumor. The variably angled lenses¹⁶¹ of the endoscope allow a wider field of view than that of an operating microscope and make it possible for the surgeon to confirm that a gross total resection has been achieved by peering around corners.³¹

Proponents of using the endoscope for the gross total resection of lesions have advised that lesions with moderate to low vascularity, soft consistency, size of less than 2 to 3 cm, low histologic grade, and location in the lateral ventricle are most amenable to resection via an endoscope.¹⁶³ The absence of hydrocephalus is not an absolute limitation to resection or an endoscopic approach to intraventricular lesions.⁷⁰ Hence,

decisions to attempt gross total resection of an intraventricular tumor must take into account the lesion's histology, size, location, and degree of vascularity. Outcome results for patients who underwent endoscopically assisted resection of pineal lesions have revealed shorter hospital stays and shorter surgical times, suggesting a potential advantage and future role for endoscopy in treating pediatric intraventricular lesions.¹⁶⁴

The most common locations for intraventricular tumor biopsies are lesions of the lateral and third ventricles as well as lesions surrounding the foramen of Monro.^{27,37,44,149,165,166} Exophytic tumors arising from the thalamus, mesencephalon, or basal ganglia may also warrant biopsy sampling; however, caution should be exercised because hemorrhagic complications during surgery may prompt conversion to an unplanned open procedure.^{155,167–169} Biopsies for intraventricular lesions are particularly useful when both CSF and tissue are needed for histologic analysis to exclude pathologies that may be amenable to radiotherapy or chemotherapy. CSF tumor markers for alpha fetoprotein and human chorionic gonadotropin may also be obtained.^{23,24} Endoscopic diagnosis of tumors like germinomas and lymphomas can alter the treatment course of children and ultimately lower the morbidity and mortality related to the surgical intervention.¹⁵⁸

Pineal Region Tumors

Pineal region tumors are one type of pediatric CNS tumor for which endoscopic biopsy is routinely used in tissue diagnosis.^{30, 155,169} Endoscopic approaches to pineal tumors have greatly enhanced the minimally invasive options for treating children with these lesions. Diagnostic biopsies with the endoscope are increasingly utilized to determine if chemotherapy, radiation, and microsurgery are warranted for a particular child's anticipated clinical course.¹⁵⁸ Pineal tumors have an incidence of 3% in the general population and comprise 11% of all pediatric tumors.¹¹⁸ Germ cell tumors are the most common pineal tumors, comprising 50 to 80% of lesions, and more than 50% of germ cell tumors are found to be germinomas. Pineal parenchymal lesions, including pineocytoma¹⁶¹ and pineoblastoma, occur in 7 to 14% of patients, and neuroepithelial lesions, such as gliomas, are the next most common diagnosis, occurring in 2 to 8% of patients. In children, 50 to 60% of tumors diagnosed with pineal tumor biopsy were found to be sensitive to chemotherapy or radiation therapy.⁵⁵

Diagnosis with this minimally invasive approach avoids the permanent morbidity of 10% associated with the open microsurgical resection of pineal lesions and the estimated 2% complication rate reported with stereotactic biopsy. In a review of the literature, endoscopy yielded a definitive diagnosis in 89% of cases, a number that may depend upon expertise among endoscopists.^{55,118} Neuroendoscopy for pineal region tumors also allows ETV for CSF diversion in the same surgical setting because 90% of patients with a pineal tumor present with hydrocephalus.¹⁵⁵ The ETV and biopsy procedure may be performed through a single bur hole, splitting the distance between a pre-coronal bur hole,¹⁵³ the site commonly used for an ETV, and a bur hole at the hairline, the site commonly used for pineal region biopsy.¹⁷⁰ A single bur hole is optimal when the lesion is anterior to a small massa intermedia and when the ventricles are dilated.

Colloid Cysts

Colloid cysts can sometimes be managed endoscopically. Colloid cysts are benign intracranial lesions and account for 1% of all intracranial neoplasms.⁴⁷ They can present with symptoms and neurologic deficits consistent with elevated ICP, and sudden death in patients, presumably from acute hydrocephalus and obstruction of the foramen of Monro, has been reported. With the increasing use of cranial MR imaging, colloid cysts are found incidentally, leaving an ongoing discussion about the parameters that necessitate operative intervention.³⁴ Traditionally, these lesions have been resected with microsurgical techniques through a transcortical and transventricular approach or a transcallosal approach.⁶² The authors prefer a bur hole that is more anterior and lateral than the midpupillary line in the endoscopic treatment of colloid cysts because this allows optimal visualization of the colloid cyst. A more medial approach may limit the resection or obscure portions of the cyst wall. Endoscopic resections have emerged as a minimally invasive treatment option for these lesions (► Fig. 11.6a,b). Endoscopic approaches are advocated because of the proposed decreases in risk of postoperative seizures from cortical manipulation, in operative time, and in hospital stay.²⁶ Open microsurgical techniques are associated with a 5% risk of seizures, whereas endoscopically guided colloid cyst removal has approximately a 1% risk for postoperative seizures. One of the most common complications of endoscopic resection that has been reported is impaired memory in 5% of cases¹⁷¹ and is attributable to manipulation of the adjacent fornices, prompting a critique as to whether the cyst capsule should be completely removed.¹⁷² Studies have also been performed on the imaging characteristics of colloid cysts and whether they dictate surgical management decisions, with hypointensity on T2-weighted MR images predicting recurrence of endoscopically resected lesions.¹⁷¹

11.4.2 Extraventricular Applications Craniosynostosis

One developing area that has generated considerable discussion¹⁷³ regarding endoscopic treatment options is craniosynostosis repair in children. Cranial remodeling for premature suture fusion is commonly performed by pediatric neurosurgeons; craniosynostosis has an estimated frequency of 0.4 in 1,000 live births. A majority of children present with involvement of single suture, most commonly the sagittal suture.^{174, 175} Surgeries involving removal of fused sutures began in the 1880s and continued to develop with more advanced techniques until the pioneering work done by Tessier in the 1970s, in which larger portions of the calvaria were removed and remodeled and fixed to allow compensatory growth. As experience with these surgeries continued to improve, certain limitations (operative time, blood loss, and the need for extended postoperative hospital admissions) became apparent. In 1999, the endoscopic approach to sagittal suturectomy was introduced and was reported to reduce the aforementioned variables. Children undergoing this treatment then required postoperative helmet orthoses to help maintain and guide desired calvarial relationships. This technique has since been adapted to other sutures, including lambdoid, metopic,

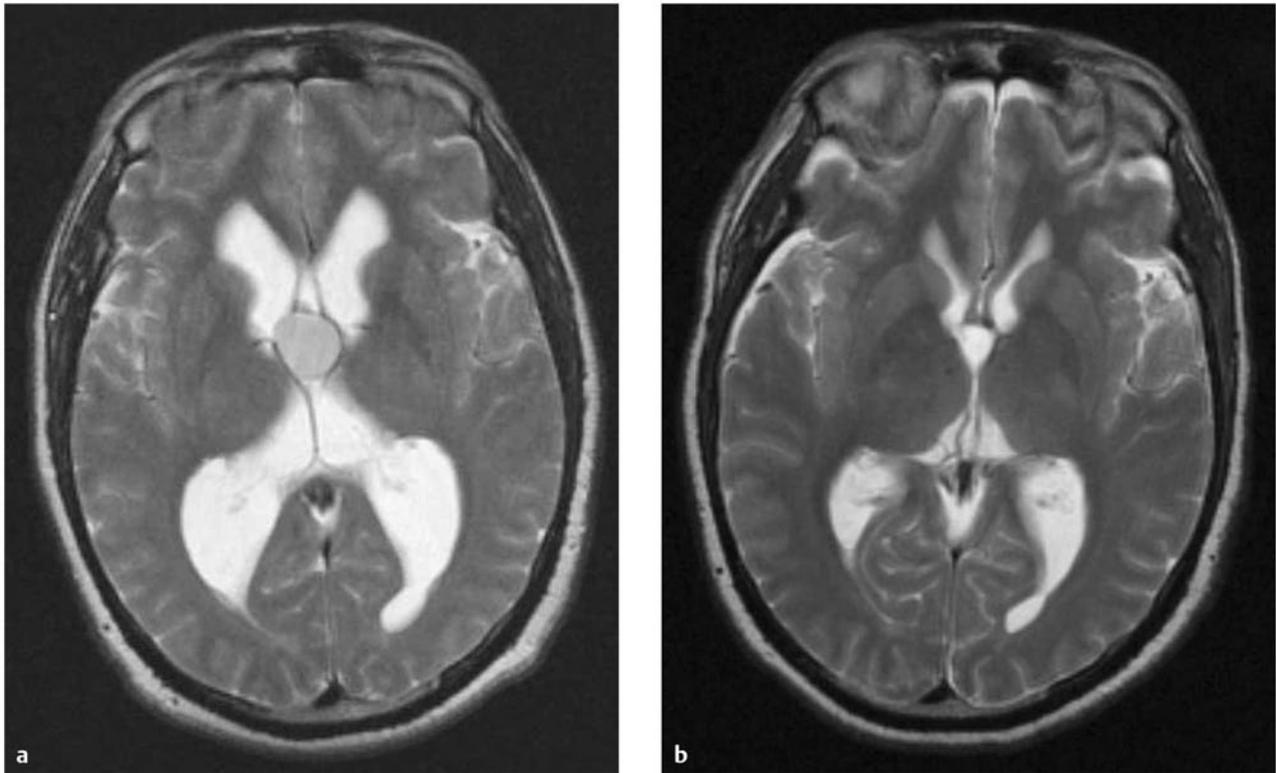


Fig. 11.6 Colloid cyst resection. (a) Axial T2-weighted magnetic resonance (MR) image of a colloid cyst with obstruction at the foramen of Monro and resulting ventriculomegaly in the lateral ventricles. (b) Axial T2-weighted MR image following endoscopic resection of the colloid cyst with a patent foramen of Monro and resolution of the ventriculomegaly.

coronal, and multisuture¹⁷⁶ forms of synostoses, with varying results. There is now extensive experience across many centers with this procedure, and reports on surgical technique continue to improve.¹⁷⁷

Surgeons advocating endoscopic correction postulate that earlier correction in children younger than 3 months of age is desirable to prevent the secondary deformational changes that accompany synostosis. The advantages of reducing blood loss and perioperative edema^{175,178} and of obtaining improved head shape based on anthropometric data¹⁷⁶ are well documented. There are, however, potential disadvantages with the endoscopic procedures that should be considered when families with affected children are counseled.¹⁷⁵ The success of obtaining a desired head shape is contingent on using helmet or band therapy and requires a family's commitment to the treatment. Ultimately, the outcomes of cranial remodeling are difficult to assess,¹⁷⁹ but parent satisfaction with endoscopy results continues to improve.

Skull Base Surgery and Endoscopic Endonasal Surgery

Endonasal approaches continue to expand the use of neuroendoscopy in pediatric neurosurgery.^{180,181} Conventional transphenoidal skull base surgery utilizes sublabial and transnasal approaches; however, in an attempt to increase the field of view and improve visualization of the sella turcica and adjacent

structures, surgeons are turning to neuroendoscopy. There are several advantages of this approach over conventional open micro-neurosurgery, including early exposure of the skull base and dura, lack of a large cranial opening and craniofacial scar tissue formation, and shorter hospitalizations. Several groups have pioneered endoscopic endonasal transsphenoidal surgery and have extended its application to address nearby pathologies by utilizing transsellar, transcribriform, transclival, and transodontoid approaches.¹⁸² The transsellar and transplanum approaches are commonly used for sella-based lesions, including pituitary adenomas, craniopharyngiomas,^{183,184} meningiomas, germinomas, and Rathke cleft cysts.¹⁸⁰ Maximizing the sphenoidotomy, posterior ethmoidectomy, posterior septectomy, and middle turbinectomy can create working space for extended surgical manipulation and the resection of lesions that previously required open craniotomies.¹⁸⁵

With endonasal approaches, it is possible to obtain openings in the sellar floor that extend from the cervical spine to the cribriform plate, while the lateral boundaries are defined by the carotid arteries, cavernous sinus, and medial orbital walls.¹⁸⁶ These exposures are not without risk, however, and require an appreciation of the carotid arteries and their relationships to the optic chiasm and pituitary gland. The optic canals serve as a landmark as they emerge in a posteromedial trajectory in the orbital apex, and the optic nerves mark the lateral limit of the transplanum approach. Other landmarks in the bone along the sellar floor include the carotid protuberances and the

optocarotid recesses, which correspond with the pneumatized portion of the anterior clinoid.^{63,185,187} Depending upon the age of the child, these landmarks may not have fully developed, and inability to appreciate the structures may make the surgery more difficult. The ethmoid sinuses enlarge by 3 years of age and are fully formed by 16 years of age, while the cavity of the sphenoid sinus starts to develop at age 4 and becomes fully developed by puberty.¹⁸ Intrasellar pathology may also expand, dehisce, and alter normal bone anatomy, shift vascular structures, or tether cranial nerves and further complicate endoscopic endonasal exposures.

Although surgeon experience with midline skull base lesions and relevant anatomy⁶³ is critical, there are lesions that obviate an endoscopic approach in children. Brain invasion, diffuse cavernous sinus involvement, encasement of the carotid arteries and cranial nerves, and extensive intradural or intraventricular extension are several factors that may necessitate a craniotomy.^{58,188} Access to these types of lesions can be difficult with angled instruments, as can adequate control of hemorrhage in the event of neurovascular injury.¹⁸ Preoperative skull base imaging with MR imaging and CT¹⁸⁹ better defines anatomical landmarks and septa in the bone leading to the exposure of the sellar floor. A careful study of preoperative images will yield a better understanding of the relationships between the normal pituitary gland, optic chiasm, hypothalamus, carotid arteries, and diaphragma sellae in relation to the lesion of interest. Stereotactic imaging⁵² identifies the midline, orients the surgeon, thereby preventing inadvertent damage to the nearby carotid arteries and optic nerves, and optimizes the extent of surgical resection for a lesion. Angled endoscopic lenses allow the surgeon to peer around corners and inspect resection beds of residual tumor.

Endoscopic endonasal surgery has had an evolving role in adult patients.¹⁸³ However, fewer studies are available in children.¹⁸⁸ The limitations of the use of endoscopic endonasal surgery in children arise from a decreased prevalence of amenable lesions and different anatomy; children have limited corridors for nasal access, with small nostrils and narrow nasal cavities, and less pneumatization of the sinuses. Because of the restricted access, a neurosurgeon and an assistant must utilize both nostrils in order to resect midline skull base lesions. The recent development of narrower-gauge endoscopes⁵⁶ may address some of the anatomical hindrances and obstacles facing the surgical team. The preoperative embolization¹⁹⁰ of larger tumors¹⁹¹ also has made it possible to expand the role of endoscopy in children and has the potential to avoid the need for larger craniofacial or transfacial approaches, which can result in facial asymmetry.¹⁸¹ Studies in children suggest that gross total resection is achievable in up to 60 to 81% of carefully selected cases for pituitary adenomas, craniopharyngiomas^{183,192,193} with sellar or infradiaphragmatic origins,¹⁸⁴ Rathke cleft cysts, juvenile nasal angiofibromas,^{182,191} and clival lesions.^{18,188} Repair of skull base defects resulting from trauma, congenital defects, or iatrogenic etiologies and leading to CSF leak is frequently addressed with endoscopic exploration and repair.¹⁹⁴

Similarly, surgeons are now more familiar with how best to address complications that arise from endoscopically assisted transsphenoidal surgeries. CSF leakage can be reduced by the application of a vascularized nasoseptal flap covering the skull base defects in order to optimize healing and can be paired

with nasal packs to buttress the repair. These measures may require the presence of a lumbar drain for CSF diversion if revision is necessary.^{181,182,193} Although limited by the decreased prevalence of the aforementioned diseases in children, endoscopic endonasal surgery in pediatric patients is feasible, and additional studies will determine the optimal parameters for selecting patients to undergo minimally invasive endoscopic approaches.

Intraparenchymal Lesions

Hypothalamic hamartoma is one type of intraparenchymal lesion that has been treated endoscopically with considerable success.¹⁹⁵ Hypothalamic hamartomas are congenital lesions that have an incidence ranging from 1 in 100,000 to 1 in 1 million and that frequently cause gelastic seizures or seizures that begin early in infancy.¹⁹⁶ Seizures from hypothalamic hamartomas are primarily refractory to current medical treatment, and patients often require surgical intervention and resection of the lesions with disconnection from the mammillary bodies.¹⁹⁷ Resection of the lesions has been found to reduce and, in most cases, to eliminate seizures.⁶⁰ Several groups have reported their results on complete or partial hamartoma resection with the neuroendoscope.^{195,198} A contralateral approach is used with the endoscope to promote visualization of the border between the lesion and the surrounding hypothalamus. In a majority of the patients treated with this approach, seizure frequency was reduced, and the seizure-free rates were not significantly different from those achieved with a transcallosal anterior interforaminal approach. The benefit of endoscopy continued to be shorter hospital stays in comparison with open microsurgery.^{196,197} Endoscopy for other epilepsy surgeries, such as corpus callosotomy and hemispherotomy,¹⁹⁹ has been illustrated in cadaveric experiments and may be amenable to translation in pediatric cases.

Several groups have utilized the endoscope to resect intraparenchymal tumors⁴⁰ in adults and children.^{59,69,164} More recently, a tubular retraction system,²⁰⁰ or port,²⁰¹ has been used to aid in tumor visualization with an endoscope-alone procedure. The port, when paired with stereotactic guidance, has been successfully employed to resect intraparenchymal lesions.²⁰² These tubular retraction systems offer the advantage of minimal retraction of the surrounding cortex with improved optics and bimanual use of instruments. Another use for endoscopy in the removal of tumors is the endoscope-assisted method^{203,204} in which the endoscope is introduced to inspect resection sites for residual tumor, to resect smaller and more inaccessible areas of tumor growth, and to look around corners.⁵⁹ Pediatric neurosurgeons continue to explore the applications of endoscopy for tumor removal in patients with various pathologies.^{27,159–161,164,198,205}

The endoscopic evacuation of spontaneous intracerebral hemorrhage is an alternative to craniotomy with hematoma evacuation.^{43,71,206,207} First described in 1985 by Auer,²⁰⁷ several studies have described the feasibility of endoscopic hematoma evacuation in adults. Endoscopy in the early stages (less than 24 hours after hemorrhage) may prevent the clotting of blood, which makes aspiration of the clot more difficult. Minimally invasive evacuation of a hematoma with an endoscope offers several advantages in decreasing the amount of injury to overlying normal

cortex, especially in the case of a deep-seated hematomas in eloquent cortex. Endoscopic approaches have been shown to shorten the surgical time, reduce the number of hospital days in an intensive care unit, and possibly improve or hasten the neurologic recovery of adult patients in comparison with patients undergoing craniotomy for evacuation.⁴³ Surgical techniques have been developed to treat intraoperative hemorrhages during clot aspiration in which surgeons remove the most distal region of hemorrhage first to prevent collapse of the cavity. Nagasaka et al describe a method combining an irrigation–coagulation suction cannula²⁰⁸ with an irrigation–suction technique. Although repeated irrigation will control small hemorrhages during surgery, an alternative method in which the combined irrigation–coagulation suction cannula is used is to identify the perforating artery with irrigation, trap it with suction, and then coagulate it. An additional method to aid inspection of a hematoma cavity is to fill the cavity with irrigation fluid and identify the bleeding arteries. Current evidence²⁰⁹ supports the endoscopic evacuation of hematomas with minimal risk and with efficacy. Future studies in children are warranted.

Finally, intracranial abscesses have been approached with various surgical treatment modalities, including stereotactic aspiration with drainage. Although not the first line in treatment options, the endoscope has been employed for abscess evacuation.¹⁵⁴ The proposed advantage of utilizing neuroendoscopy coupled with stereotactically guided aspiration is that the surgeon is able to visualize the drainage to ensure complete evacuation. Endoscopy may be advantageous in the event of multiseptate abscess or subdural empyemas, or in the intraventricular evacuation of purulent material. Few studies using endoscopy have been performed, and additional studies will be required to determine its effectiveness in treating intracranial abscesses.²¹⁰

11.4.3 Other Applications

Spinal applications^{194,211–213} for endoscopy continue to expand each year, with the focus on minimally invasive treatment of spinal pathologies. Endoscopy has been utilized in the treatment of herniated intervertebral disks,^{214,215} placement of spinal instrumentation,²¹⁶ treatment of idiopathic scoliosis,²¹⁷ fenestration of intramedullary spinal cysts,²¹⁸ suboccipital decompression for Chiari malformation,²¹⁹ transnasal odontoidectomy,⁵⁷ transoral and transcervical approaches to the craniovertebral junction,^{220–222} and intradural resection of spinal cord tumors and split-cord malformations.²¹¹ Although larger studies for each application are warranted to determine efficacy, the neuroendoscope is not limited to cranial applications in children.

11.5 Complication Avoidance and Management

One of the essential aspects of working with neuroendoscopy is to realize its limitations²²³ when surgeons are manipulating tissues in limited corridors deep within the brain. Rapid access to these areas of the CNS can be hindered by the presence of adjacent critical neural structures and eloquent cortex. Potential intraoperative complications²²⁴ and strategies for their management should be considered before their occurrence and a contingency plan should be identified should additional meth-

ods be required.¹¹⁴ Although the previous sections have illustrated the diverse set of neuroendoscopic applications and a promising future in addressing a variety of pathologies, great care must be taken to consider the neurovascular implications of injury to adjacent structures.²²⁵

One of the most common intraoperative complications during intraventricular neuroendoscopy is hemorrhage,⁵⁵ which can vary in severity depending upon the size of the arteries or veins disturbed during surgical manipulation. Intraventricular hemorrhage is a nuisance in endoscopic procedures because the clear anatomy quickly becomes opacified and surgical navigation within the ventricle is hindered. Identification of the source of the bleeding is the first step to stopping the hemorrhage and clearing the operative view.^{121, 150, 152} Hemorrhage may result from injury to small cortical vessels during introduction of the endoscope into the ventricles or manipulation at the cortical surface. In addition, small perforators may be damaged during the manipulation of intraventricular lesions, such as colloid cysts and tumors,¹⁶⁶ or during ETV.^{81, 96} These small-vessel hemorrhages, even if persistent, usually respond to tamponade with the endoscope or balloon catheter⁷⁰ or to gentle irrigation. Electrocautery may be used if the vessel can be seen at the cortical surface, and persistent irrigation within the ventricle may help identify a deeper source of bleeding. Bipolar electrocautery may also be employed if the hemorrhage is more brisk.⁷³

When a more persistent torrent of blood is seen, a larger vessel has been injured, and gentle and persistent irrigation may not be adequate to stop the source. If after persistent irrigation the field continues to be filled with blood and identification of the source is not possible,²²⁶ there is the option to convert the procedure to an open craniotomy, widening the exposure and introducing the surgical microscope by creating a small craniotomy followed by placing a ventriculostomy to aid in the drainage of blood products. However, leaving a ventriculostomy²²⁷ when the surgical field has occasional small areas of hemorrhage and adequate hemostasis has not been obtained may place children at additional risk for persistent intracranial hemorrhage.¹²⁰ The ventriculostomy will allow drainage and measurement of the ICP¹⁰⁷ for an early warning of persistent intraventricular hemorrhage. Thankfully, with experience, conversion² to an open procedure is not a frequently encountered problem; however, before surgery, contingency plans for such an event should be made. Early postoperative cranial imaging with head CT is recommended should there be an area of concern. If a large vessel like the basilar artery⁷⁵ has been compromised during neuroendoscopy, then endovascular approaches may be required, and the appropriate consultation should be obtained for emergency evaluation.

An additional aspect to working with endoscopes that is persistently encountered is failure of the equipment during a procedure.⁵² The lenses of the endoscope may become compromised along with the digital imaging; in addition, sheaths, endoscopes, and microinstruments may be bent or impossible to place in the appropriate port for use. If these situations occur, backup instrumentation and scopes should be readily available. Proper maintenance and training in the handling of endoscope equipment for all staff should help to minimize equipment failure. The surgeon should also have a routine for checking that the equipment is available, intact, and connected in the proper

orientation before making an incision or introducing the endoscope into the CNS. This may help to prevent excess manipulation in and out of the brain.⁸⁷

Loss of orientation may occur during surgery and may result from failure to check the proper lens orientation before placing the scope in the sheath, utilizing an inappropriately angled lens, or failure of the stereotactic localization. Hemorrhage and unfamiliar anatomy may also lead to error. If disorientation occurs, it can lead to mistaking the anatomy of the ventricle and placing the ETV posteriorly and 180 degrees from the desired location. Similarly, during cyst fenestrations, tissue adjacent to the stoma may serve a critical function in the thalamus or globus pallidus.^{133,140,228} Stereotactic localization may aid in preventing missteps.⁵³ Irrigation may also be used to test the movement of the underlying tissue to help determine whether the tissue is solid or part of a cyst wall. If the stereotactic localization has been compromised, anatomical landmarks become crucial, and the foramen of Monro and choroid plexus, if present, may serve as beacons for orientation. In addition, surface anatomy of the zygoma, sagittal suture, midpupillary line, tragus, andinion may be utilized to verify location and orientation during surgery. The surgeon should cease advancing the surgical instruments should disorientation occur and attempt to re-establish familiar landmarks.

11.6 Conclusion

Applications of neuroendoscopy continue to emerge rapidly in pediatric neurosurgery and have a promising future. As minimally invasive approaches achieve maximal and favorable outcomes, more and more surgeons are adopting these techniques for the care of their pediatric patients. Although endoscopic applications continue to push the limits and offer exciting new areas of investigation and instruments for surgical resections, restraint is needed until their efficacy²¹³ in children has been determined. The technology has outpaced our understanding of the clinical outcomes in certain areas⁸³ of pediatric neuroendoscopy, and we are charged with validating early studies with future work. Additional discourse and surgeon training will help to establish guidelines for training¹⁷³ and for patient selection.^{14,37,42,74,79,113,175}

Pearls

- The role of neuroendoscopy for the treatment of various pediatric neurosurgical diseases, which include intraventricular tumors, cyst fenestrations, and craniosynostosis, continues to expand. Neuroendoscopy also has applications in intraparenchymal procedures, skull base surgery with endonasal approaches, and spinal surgery.
- Anatomical landmarks should be identified and serve as beacons throughout a procedure. Such structures include the choroid plexus of the lateral ventricles, the foramen of Monro, the fornices, and the cerebral aqueduct.
- A preoperative routine of checking the instruments and orientation of the lenses will help avert missteps and disorientation intraoperatively.
- Management of potential complications should be considered before surgery so that a contingency plan is in place.

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12 Intraventricular Hemorrhage and Post-Hemorrhagic Hydrocephalus

Jeffrey R. Leonard and David D. Limbrick Jr.

Intraventricular hemorrhage (IVH) remains the most common severe neurologic complication of preterm birth and presents significant life-long challenges for affected individuals. Approximately 12.1% of children born in the United States are born preterm, and very low-birth-weight infants are the most likely to develop IVH.¹ At the time of its publication in 1978, the landmark paper by Papile et al documented that 45% of low-birth-weight infants developed IVH.² Although marked improvements in medical care of the newborn have resulted in considerably lower IVH rates (currently 15 to 20%), the neurologic outcomes of infants who experience IVH are among the worst in neonatal medicine.^{3,4} Post-hemorrhagic hydrocephalus (PHH) occurs in up to one-half of those with IVH and is associated with a three- to fourfold increase in the risk for cognitive and psychomotor disability. Infants with PHH who require ventriculoperitoneal (VP) shunts have the worst neurologic outcomes, however, with neurodevelopmental impairments observed in more than 85% of infants and cerebral palsy in nearly 70%.⁵ In the current chapter, we review the recent literature regarding state-of-the-art diagnostic modalities, surgical and nonsurgical treatments, and outcomes observed in treating this disease. For additional information on the topics discussed herein, we refer the reader to the recent comprehensive review published by Dr. Shenandoah Robinson.⁶

12.1 Epidemiology

In tracking the effect of advances in antenatal, perinatal, and neonatal care over the past two decades, the Neonatal Research Network recently reported a survival rate of 92% for infants born before 28 weeks' postmenstrual age (PMA).⁴ IVH occurred in 16% of very preterm infants, with the incidence of IVH demonstrating an inverse correlation with PMA.⁴ The classification of IVH in premature infants is listed in ► Table 12.1. At 22 weeks' PMA, 30% of preterm infants had IVH; conversely, at 28 weeks' PMA, only 3% of patients had IVH.⁴ When the incidence of IVH in preterm infants was considered by grade,² 48% were classified as having grade 1 IVH, 18% had grade 2 IVH, 15% had grade 3 IVH, and almost 19% had grade 4 IVH.⁷ Although reports vary somewhat, it is estimated that 25 to 50% of infants with IVH develop post-hemorrhagic ventricular dilatation requiring neurosurgical treatment.⁸ As previously noted, severe IVH is associated with significant neurologic disability, particularly in those infants who develop PHH and require a VP shunt.⁵ These children frequently have severe cognitive impairments, cerebral palsy,⁹ and in many cases seizure disorders.^{1,10}

12.2 Pathophysiology

Alterations in blood flow to the developing germinal matrix microvasculature are believed to be the pathophysiologic

Table 12.1 Classification of intraventricular hemorrhage in premature infants

Grade	Hemorrhage location	Ventricular involvement
Grade 1	Germinal matrix hemorrhage	< 10%
Grade 2	IVH with no ventricular expansion	< 50%
Grade 3	IVH with ventricular expansion	> 50%
Grade 4	Extension into parenchyma	

Abbreviation: IVH, intraventricular hemorrhage.

Source: Adapted from Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92(4):529-534.²

basis of IVH in premature infants.⁸ At the age when IVH is most likely to occur, key elements of the blood-brain barrier, including tight junctions, basement membrane, glial foot processes, and other supporting cellular structures, remain incompletely developed, leaving microvessels susceptible to disruption.¹² Thus, when hypotension, hypoxemia, or other systemic insults occur, corresponding changes in cerebral blood flow in the germinal matrix may result in hemorrhage into the surrounding tissue and/or the ventricle. In support of this concept, a retrospective case-control study matching premature infants with and without hypotension found that hypotension was a risk factor for the development of IVH and neurologic injury.¹³ Furthermore, if significant parenchymal hematoma is present, particularly in combination with ventricular distention, parenchymal infarction also may occur (grade 4 IVH).⁸

In cerebrovascular development, vessel growth and maturation progress from the pial surface and extend into the parenchyma, a factor that may contribute to the susceptibility of the deep white matter to hypoperfusion during the newborn period.¹⁴ Additionally, the capacity for autoregulation, which is mediated primarily by small cerebral resistance vessels, develops relatively late, limiting the ability of these small vessels to attenuate alterations in cerebral blood flow.^{15,16} Data from experimental models confirm this temporal sequence, with regulation of blood flow to the germinal matrix improved with increasing gestational age.¹⁷

In the setting of hypotension, hypoxemia, hypercapnia, or acidosis, cerebral blood flow appears to be affected to a large degree by inflammatory mediators like transforming growth factor- β (TGF- β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and other factors that affect the cyclooxygenase pathway (COX-2).⁶ Proinflammatory molecules affect not just cerebral blood flow but also blood-brain barrier permeability via the disruption of tight junctions and specific barrier proteins.¹² Growth factors, cytokines, nitric oxide, and other molecules mediate these and other events, such as leukocyte endothelial

transmigration and activation of microglia; in turn, reactive oxygen species are produced that cause endothelial injury and parenchymal infarction.^{18,19}

Evidence is accumulating to suggest that genetic factors also may play a role in IVH. Gould et al have shown that mutations in the collagen 4A1 gene result in IVH in experimental models and are associated with hemorrhage and porencephaly in infants.^{20,21} Additionally, genetic mutations associated with thrombophilic conditions, such as mutations in the genes for prothrombin and factor V Leiden, also have been implicated in IVH and porencephaly.^{22,23} Finally, polymorphisms or mutations in the genes for proinflammatory cytokines, such as IL-6 and TNF- α , may also be involved in the pathogenesis of IVH, although this is controversial.^{24–26} It is likely that additional candidate genes with etiologic involvement in IVH will be identified in the near future.

The mechanism(s) by which IVH results in hydrocephalus (PHH) remains to be determined. Although PHH may have both obstructive and nonobstructive components, the condition generally results at least in part from impairment of cerebrospinal fluid (CSF) absorption at the level of the arachnoid villus or other absorptive pathway. In preterm infants, arachnoid granulations are immature and thus capable of undergoing robust fibrosis from the blood products or inflammatory mediators associated with IVH.²⁷ Blood degradation products and debris are thought to initiate an inflammatory process consistent with chronic arachnoiditis whereby laminin, collagen, and other extracellular proteins are deposited throughout the ependyma and subarachnoid spaces.²⁷ TGF- β and other cytokines, together with free radical elaboration, trigger a cascade of arachnoid fibrosis and ependymal–subependymal gliosis.²⁸ In support of this hypothesis, infants with PHH have been found to have significantly higher levels of TGF- β_1 and an aminoterminal propeptide of type 1 collagen in their CSF.^{29,30} Vascular endothelial growth factor (VEGF) has also been implicated in the pathogenesis of PHH, although its role is less well understood.¹² In many cases, this inflammation-based impairment of CSF absorption is compounded by ventricular outflow obstruction due to blood clots and debris within the ventricular system.

The effect of IVH and PHH on neurodevelopment is multifactorial. The period in which IVH occurs (before 34 weeks' PMA) is a critical neurodevelopmental interval, and neurologic injury during this time is likely to impair the proliferation and migration of neural precursors, neurite outgrowth and myelination, and functional network development.³¹ Clearly, the combination of ischemia–infarct and hematoma in germinal matrix is likely to cause significant injury to the nests of glial and neural precursor cells that reside in the subependymal zone.³¹ Furthermore, inflammation, cellular infiltration, and the generation of free radicals cause damage to the periventricular white matter and contribute to scarring and leukomalacia.^{32,33} Particularly in the setting of PHH, local increases in pressure and anatomical parenchymal distortion may affect development in the adjacent periventricular region, while a global increase in intracranial pressure (ICP) may impair cerebral perfusion and cause ischemia.⁶

12.3 Clinical Presentation

IVH may range from clinically silent to catastrophic, but most cases that go on to require neurosurgical attention take a

Table 12.2 Expected symptoms in neonates with hydrocephalus

Fontanel	Full, tense, nonpulsatile
Sutures	Split
Head circumference	Crossing percentile curves
Systemic symptoms	Irritable, less active, apnea, bradycardia

saltatory course, with hemorrhage occurring within the first hours to days after birth and then progressing for days to weeks.^{3,6} IVH is frequently diagnosed via screening cranial ultrasound and then monitored clinically. Although IVH may be associated with neurologic changes (e.g., decreased level of arousal, motor asymmetry, hypotonia, others), the development of PHH and thus increased ICP is heralded by changes in cranial parameters, including a bulging fontanel, increasing head circumference, and splaying of the cranial sutures. All of these metrics are examiner-dependent and somewhat subjective, but splaying of the sagittal suture may be the most reliable indicator.⁶ Later in the disease course, nonspecific but serious signs, such as apnea, bradycardia, and decreased spontaneous activity, may be observed (► Table 12.2). In cases of rapidly expanding hydrocephalus, ventricular enlargement may outpace increases in head circumference because of the relative compressibility of the white matter.³⁴

12.4 Imaging of Neonatal Hydrocephalus

At many centers, cranial ultrasonography is the primary imaging modality used to screen preterm infants for IVH. Cranial ultrasonography avoids ionizing radiation, is performed at the bedside, and permits adequate visualization of intracranial hemorrhage within the neonatal intensive care unit. The American Academy of Neurology practice parameter for neuroimaging of the neonate states that cranial ultrasonography should be performed at two time points (7 to 14 days and 36 to 40 weeks' PMA) to look for IVH, ventriculomegaly, and/or periventricular leukomalacia.³⁵ Widely accepted measurements of ventricular size used in preterm infants include the ventricular index,³⁶ anterior horn width, and thalamo-occipital distance.³⁷ Normative data for these ventricular measures in the preterm infant are available; however, the optimal threshold for clinical treatment has not been determined.^{36,37}

Magnetic resonance (MR) imaging is the method of choice for providing anatomical detail in the developing brain. Computed tomography (CT) is generally avoided when possible in the preterm infant because of the risks associated with repeated exposure of the developing brain to radiation.³⁸ Conventional T1- and T2-weighted MR sequences provide high-resolution images of the ventricular system and of cortical and subcortical structures, and MR imaging has become an essential part in the evaluation of neurologic injuries and congenital malformations in the newborn. In recent years, advanced MR imaging techniques, such as diffusion tensor imaging (DTI), also have been developed to assess subtle alterations in white matter integrity that remain undetected by conventional MR imaging sequences. Diffusion tensor imaging measures the magnitude and

directionality of water displacement in tissue and provides quantifiable measures of diffusion, fractional anisotropy, and mean diffusivity. Fractional anisotropy shows an exponential increase with neurodevelopment, whereas mean diffusivity shows a corresponding decrease during this interval.³⁹ Deviation of fractional anisotropy and the apparent diffusion coefficient from normative values is indicative of white matter damage, as demonstrated in various neurologic disorders, including hydrocephalus.^{40,41} Whereas DTI is used to examine static white matter microstructure, resting-state functional connectivity MR imaging (fc MRI) utilizes low-frequency (<0.1 Hz) fluctuations in the blood oxygen level-dependent (BOLD) signal to explore the functional neuronal networks.^{42,43} Although preliminary, fc MRI is now being applied in preterm infants to study the effect of newborn brain injury on functional cerebral architecture, and specifically the effect of pressure-based deformation in PHH on short- and long-term neurologic outcomes.

12.5 Clinical Treatment

12.5.1 Prevention as Treatment for Post-Hemorrhagic Hydrocephalus

Prevention of IVH and thus PHH is a primary goal in care of the preterm infant, and significant progress has been made in this regard. As noted above, a number of risk factors for IVH have been identified: early PMA and maternal hemorrhage/infection/inflammation, history of sepsis, hypotension, hypoxemia, hypercapnia, acidosis, pulmonary hemorrhage or pneumothorax, and respiratory distress syndrome (reviewed by McCrea and Ment).¹² It follows that prevention of IVH is best achieved by preventing or mitigating these conditions. Of particular interest, lack of antenatal steroid treatment during preterm labor has been shown to be a risk factor for IVH, and a number of studies have shown that antenatal steroid administration reduces the risk for IVH.⁴⁴ The mechanisms underlying this finding remain to be determined; however, it is likely that steroids attenuate increases in cerebral blood flow at the level of the germinal matrix through their effect on COX-2 and prostaglandins and assuage the inflammatory cascade that results in further disruption of the developing blood–brain barrier.¹² Additionally, steroids promote maturation of the immature choroid plexus.⁴⁵ Of note, however, a recent publication suggests that *postnatal* corticosteroids may increase the risk for neurodevelopmental difficulties with no associated reduction in risk for IVH, periventricular leukomalacia, or mortality.⁴⁶

A number of other pharmacologic agents have been evaluated for their ability to prevent IVH (► Table 12.3). Phenobarbital, which prevents fluctuations in blood pressure and is thought to mitigate free radical-mediated injury, has been extensively investigated.¹² Whitelaw and Odd performed a meta-analysis of 10 trials and found no reduction in IVH or PHH.⁴⁷ Reduction of IVH was observed serendipitously when indomethacin, a COX inhibitor, was used to close patent ductus arteriosus in newborns. Indomethacin was believed to facilitate germinal matrix vessel maturation,⁴⁸ improve cerebral autoregulation,⁴⁹ and decrease ischemia.⁵⁰ Indomethacin was investigated formally for use in preventing IVH. Although rates and severity of IVH were indeed lower with indomethacin, the effect on

Table 12.3 Pharmacologic agents used for intraventricular hemorrhage

Effect on IVH	Agent	Effect on neurodevelopmental outcome
No effect	Phenobarbital	None
	Ibuprofen	None
	Postnatal steroids	Worsened
Decrease risk	Indomethacin	Unclear, may improve in males
	Antenatal steroids	Improved
	Vitamin E	None
	Ethamsylate	None
	Pancuronium (Pavulon)	None

long-term neurologic outcome is less clear.⁵¹ In one trial, despite a decrease in IVH, no improvement in survival or neurosensory outcome was observed.⁵² A second trial demonstrated benefit in decreasing IVH rates and severity and increasing neurodevelopmental test performance in males only. Fowlie et al recently published an update of their meta-analysis of the effect of indomethacin on IVH.⁵³ The COX inhibitor ibuprofen has a mechanism of action similar to that of indomethacin and appears to improve cerebral autoregulation in animals. In clinical trials, however, ibuprofen was ineffective in reducing IVH.⁵⁴

Other pharmacologic agents evaluated for the prevention of IVH include vitamin E, ethamsylate, and pancuronium (Pavulon). Through different mechanisms, each has been shown to decrease the incidence of IVH, but not mortality or neurologic impairments (reviewed by McCrea and Ment).¹²

12.5.2 Therapeutic Removal of Cerebrospinal Fluid via Lumbar Puncture for Post-Hemorrhagic Hydrocephalus

The efficacy of serial lumbar punctures for the treatment of PHH has been investigated extensively and also has been reviewed as part of the Cochrane Library.⁵⁵ Kruesser et al (1985) initially reported using lumbar punctures (optimally 10 mL/kg per lumbar puncture) to decrease ventricular size in patients with post-hemorrhagic ventricular dilatation.⁵⁶ A number of studies followed, including four prospective clinical trials, to investigate the effect of CSF removal on survival, hydrocephalus and requirement for a VP shunt, and neurodevelopmental outcome. Evaluating these data is difficult because of considerable variation in the subject enrollment criteria, the interventions themselves (some used lumbar punctures, some used ventricular tapping; the volume of CSF removed was inconsistent and often insufficient), and imprecision in the description of neurodevelopmental outcomes. However, meta-analysis of the available data failed to show a significant benefit of CSF removal in reducing the need for shunt surgery or neurologic disability.⁵⁵ Nonetheless, lumbar punctures continue to be used clinically in infants showing obvious signs of increased ICP or as a temporizing measure in infants about to undergo placement of a ventricular access device. In such scenarios, 10 to 20 mL/kg is typically removed to decrease ICP; however, fibrosis or other factors often reduce the volume of CSF that can be removed.

12.5.3 External Ventricular Drainage

Concurrent with studies evaluating lumbar punctures for PHH, external ventricular drainage (EVD) was proposed as a method for the continuous management of hydrocephalus and control of ICP. One series reported on 37 infants with PHH treated with EVD for a mean of 21 days. Of these, 68% required VP shunts, but 67% had normal cognitive function and 33% had normal motor function.⁵⁷ Although EVD continues to be used at some centers,⁵⁸ this method has not reached widespread acceptance for the management of PHH, presumably because of the risk for infection and technical concerns regarding the integrity of the scalp in the preterm infant. The latter concern was recently addressed in a technical report in which a modified umbilical vessel catheter was used as an EVD in this setting.⁵⁹

12.5.4 Diuretics

Because of the discouraging results from the studies investigating CSF removal described above, efforts were refocused on the pharmacologic treatment of post-hemorrhagic ventricular dilatation. Diuretics were utilized because of their potential to reduce CSF production.²⁷ Early studies investigating acetazolamide, an agent already in use for this purpose in idiopathic intracranial hypertension, reported encouraging results⁶⁰; however, a large multicenter randomized controlled trial utilizing acetazolamide and furosemide for post-hemorrhagic ventricular dilatation demonstrated no benefit to using these agents in terms of survival or need for shunt surgery in post-hemorrhagic ventricular dilatation.⁶¹ Furthermore, diuretic therapy was associated with marginally worse motor outcomes at 1 year and nephrocalcinosis. Ultimately, a Cochrane Library meta-analysis showed that diuretic use was neither safe nor effective in the treatment of PHH.⁶⁰

12.5.5 The DRIFT Trial: Early and Late Outcomes

The concept of DRIFT (*drainage, irrigation, and fibrinolytic therapy*) grew out the belief that the optimal treatment of post-hemorrhagic ventricular dilatation would not just reduce ICP but would also eliminate injurious intraventricular blood and blood breakdown products (e.g., iron) and proinflammatory cytokines. The DRIFT treatment involved placement of right frontal and left occipital ventricular catheters and then injection of low-dose tissue plasminogen activator, which was left in the ventricle for 8 hours. After the 8-hour interval, artificial CSF was continuously infused through the right frontal catheter, with egress of the fluid through the left occipital catheter set to maintain the ICP at 7 mm Hg. The infusion was continued until the CSF cleared, usually in 3 to 7 days.⁶²

The short-term outcomes (up to 6 months of age or at hospital discharge) from this randomized controlled trial showed no reduction in shunt surgery or death in the DRIFT intervention arm. At interim analysis, the trial was stopped because of suspected treatment futility and an association of DRIFT with secondary IVH. In the long-term follow-up study, however, DRIFT was associated with a reduction in cognitive disability in

survivors; 31% of infants had severe cognitive disability in the DRIFT group versus 59% in the conventional treatment group.⁶³ These results have sparked a number of research efforts investigating optimal treatment approaches for post-hemorrhagic ventricular dilatation.

12.5.6 Temporizing Neurosurgical Procedures for Post-Hemorrhagic Hydrocephalus

Ventricular Reservoir

In infants weighing less than 2 kg, a temporary ventricular access device is often inserted for the purpose of treating PHH. Perhaps the most common type of ventricular access device, the ventricular reservoir was first described in 1983 by McComb et al.⁶⁴ Once implanted, ventricular reservoirs allow serial percutaneous access of the ventricular system. Serial taps for CSF removal are then used to treat clinical and radiographic signs of elevated ICP. In general, the volume of CSF removed is 10 mL/kg per tap (although up to 20 mL/kg is considered acceptable and safe). The volume removed and the frequency of removal are then tailored to each infant based on vital signs, physical parameters (head circumference, tenseness of the anterior fontanel, and splaying of sutures), and ventricular measures obtained from serial cranial ultrasound studies or other imaging. Others have reported using flow velocities on transcranial Doppler ultrasound to guide the appropriate timing and volume of CSF removal for PHH.⁶⁵

Ventriculosubgaleal Shunt

Ventriculosubgaleal shunts (VSGSs) are an alternative method for drainage of the CSF and treating PHH-related increases in ICP.^{66,67} A VSGS comprises a ventricular catheter connected through a right-angle device to a small segment of distal catheter that is inserted into a large subgaleal pocket. Some surgeons include an in-series reservoir to permit tapping in the event of VSGS failure or a distal slit valve to provide limited back pressure and encourage physiologic CSF absorption. VSGSs provide continuous drainage of CSF into the subgaleal space and thus, in theory, maintain the ICP within a normal range on a constant basis. VSGSs are closed systems; tapping is not required, and fluid and electrolytes are not lost. Furthermore, because tapping is not required, VSGSs offer the potential for earlier hospital discharge with close follow-up. Like reservoirs, VSGSs have very low infection rates, although this rate may vary up to 6%.⁶⁸ Of note, the life span of a VSGS is generally longer than 30 days, and after this interval, if the hydrocephalus has not resolved, the surgeon can opt to revise the VSGS (usually reopening the scarred-in subgaleal pocket) or to place a permanent VP shunt.⁶⁷

To date, no study has demonstrated an advantage of VSGSs over ventricular reservoirs. Wellons et al (2009) presented their results from a four-center retrospective review of preterm infants being treated for PHH.⁵⁸ In their series, 31 of 36 subjects (86%) initially treated with VSGSs required permanent VP shunting, compared with 61 of 88 (69%) treated with ventricular reservoirs. The difference in the shunt placement

rates was statistically significant, suggesting that infants treated with ventricular reservoirs may have a lower rate of shunt dependence. A recent study at our institution found that the rates of shunt infection, shunt revision, and need for permanent shunt placement did not differ between patients with VSGSs and those with ventricular reservoirs.⁶⁹ Consistent with the findings of Lam and Heilman, the observed rate of permanent VP shunt implantation in our series was lower in the VSGS group (66.7% vs. 75.4%, $p=0.38$), although this difference was not significant.⁷⁰ The selection of type of temporizing neurosurgical procedure (ventricular reservoir vs. VSGS) remains controversial and is the subject of an ongoing prospective clinical trial through the Hydrocephalus Clinical Research Network (Shunting Outcomes in Post-Hemorrhagic Hydrocephalus, or SOPHH).

Also controversial is the timing of intervention for PHH. At present, no evidence-based guidelines exist to inform the decision of whether or when to intervene in PHH. Two multi-institutional, retrospective studies from a cooperative Dutch neonatal network focused on early treatment of PHH with CSF removal via lumbar punctures or ventricular reservoirs. Both reports demonstrated lower rates of neurologic disability and shunt dependence if CSF removal was initiated when ventricular size reached the 97th percentile^{71,72} rather than the 97th percentile + 2 standard deviations. The first study⁷¹ included 95 infants with post-hemorrhagic ventricular dilatation, 22 of whom did not develop progressive PHH. Five of 31 infants (16%) in the early treatment group and 26 of 42 infants (62%) in the late treatment group required VP shunts.⁷¹ Moreover, the number of infants with moderate or severe handicap was lower in the early treatment group (16%) than in the late treatment group (26%). The second study showed shunt dependence rates of 27.2% and 72.7% for the early and late intervention groups, respectively.⁷² The developmental quotient was also significantly lower in the late intervention group. Of note, both of these studies used lumbar punctures almost exclusively, rather than ventricular access devices, and the authors acknowledge that lumbar punctures were frequently insufficient to achieve the standard volume of 10 mL/kg per tap. Thus, these reports may underestimate the true impact of early intervention on shunt rate and neurologic deficit. Based in large part on these data, an international, multi-institutional prospective randomized controlled trial examining early treatment of PHH is currently under way (Early versus Late Ventricular Intervention Study, or ELVIS).

Ventriculoperitoneal Shunts

Placement of a VP shunt is the permanent solution for the diversion of spinal fluid. Often, patients who have a shunt placed during their prenatal period have problems with malfunctions.⁷³ Some have shown that shunt failure can occur in up to 12.6% of cases within the first 3 months of shunt placement.⁷⁴ For these reasons, the timing for initial shunt placement has been extensively studied. Most believe that a shunt should be placed once the patient reaches a weight of approximately 2 to 2.5 kg. Some advocate that the protein level should be less than 1.5 g/L, as well.²⁷ However, the data are mixed, with

another single-institution study showing no correlation between failure rates and spinal fluid protein and glucose levels. Hemorrhage and inflammation can also complicate shunt placement in these infants and can often lead to trapped ventricles. Depending on the site of obstruction, cranial nerve findings, ataxia, and changes in vital signs may develop. These situations often require the placement of complicated shunt systems, although neuroendoscopy both at our institution and others has become an accepted treatment for patients with these complicated problems.

12.5.7 Endoscopic Third Ventriculostomy

Some have advocated the use of endoscopic third ventriculostomy (ETV) with or without choroid plexus coagulation in the treatment of PHH.⁷⁵⁻⁷⁷ Although the complication rate in experienced hands is low, the data reported thus far have not shown ETV to be particularly effective in treating PHH, with fewer than 50% of procedures being successful.^{77,78} In a recent publication, Warf and colleagues demonstrated the importance of the prepontine cistern status (i.e., scarring present in the cistern) and the predictive value of FIESTA (fast imaging employing steady-state acquisition) MR imaging in applying ETV to PHH. Four of 10 patients in this study required no further shunt surgery, and the absence of scarring within the prepontine cistern correlated with a good outcome.⁷⁵ In a paper relating success of ETV to hypoabsorption, Lipina et al were successful in 37.5% of their patients with PHH, and they found that low levels of TGF- β_1 correlated with successful ETV.⁷⁹ ETVs with or without choroid plexus coagulation may prove to be useful in selected patients; limited data exist, however, to advocate the widespread use of this procedure at this time.

12.5.8 Toward Improving the Outcome of Infants with Post-Hemorrhagic Hydrocephalus

A major shortcoming limiting efforts to improve the treatment of PHH is the lack of quantifiable metrics to inform clinical decision making. Biomarkers are emerging in various fields as valuable predictors of clinical course and therapeutic response.⁸⁰⁻⁸² In the future, protein markers in CSF, blood, or urine and non-invasive techniques such as DTI, fc MRI, and quantitative MR angiography in particular may serve as useful metrics for use in the standardization and optimization of PHH treatment.⁸³ Elevated levels of nerve growth factor (NGF), neurotrophin-3 (NT-3), vascular endothelial growth factor (VEGF), erythropoietin (EPO), and soluble FAS have been observed in pediatric hydrocephalus of various types,⁸⁴⁻⁸⁷ and TGF- β elevations have been identified in PHH.^{29,88} More recently, advanced high-throughput proteomics techniques have been used to study CSF from infants with PHH, and a number of new candidate CSF markers of PHH and PHH-related neurologic disability have been identified, including L1CAM, APP, NCAM1, and brevican.⁸⁹ Such markers may be used to complement existing ventricular measures in order to optimize the timing of therapeutic intervention

or to monitor therapeutic response. Real-time functional data also may be obtained from amplitude-integrated electroencephalographic (aEEG) monitoring of ongoing cerebral electrical activity in the preterm infant. Olischar et al (2004, 2008) have suggested that aEEG tracings demonstrate characteristic changes as ventricular dilation progresses.^{90,91} This technology is particularly compelling as it may be useful in signaling real-time physiologic changes in advance of anatomical changes of PHH observed on imaging.

Pearls

In these authors' experience:

- The likelihood of progressive hydrocephalus after IVH increases with the hemorrhage grade.
- Early and aggressive intervention in the premature infant may decrease the need for a VP shunt and/or improve neurologic outcomes.
- Shunt malfunctions are extremely common in patients with IVH.

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13 The Dandy-Walker Complex and Arachnoid Cysts

Hugh J. L. Garton

13.1 Dandy-Walker Complex

The Dandy-Walker complex is a heterogeneous group of anatomically and possibly embryologically related disorders that have in common a distortion of midline cerebellar anatomy and a large posterior fossa cyst, usually in communication with the fourth ventricle. The complex often appears in conjunction with other central nervous system (CNS) abnormalities, especially agenesis of the corpus callosum. Pathologically, the enlarged posterior fossa fluid collection can expand, compressing other posterior fossa structures and producing hydrocephalus. Surgical management is usually directed at treating the hydrocephalus or the posterior fossa cyst, or both, either by cerebrospinal fluid (CSF) shunt diversion or by endoscopic techniques.

13.1.1 Anatomy and Pathogenesis

Anatomy

Three described and likely related entities, (1) Dandy-Walker cyst (DWM), (2) Dandy-Walker variant (DWV), and (3) persistent Blake pouch, have been lumped together as Dandy-Walker complex (DWC). A fourth diagnosis, mega cisterna magna, may belong, as well¹⁻⁴ (► Fig. 13.1). In addition, midline posterior fossa arachnoid cysts are frequently part of the differential diagnosis of posterior fossa cystic lesions.

Anatomically, DWM consists of a large cystic fluid collection that appears to arise out of an expanded fourth ventricle with an associated lack of the cerebellar vermis. The posterior fossa is typically enlarged, with elevation of the tentorium and the torcular herophili and associated confluence of the venous sinuses. The cerebellar hemispheres are present, although they may be compressed by the cyst, which may also compress the brainstem. The aqueduct of Sylvius is variably obstructed. Hydrocephalus is present in many, although not all, patients and may be present with or without an obstructed aqueduct.^{1,4} Radiographically, initially based on axial computed tomography (CT), DWM came to be defined as an entity in which no apparent vermis was present. DWV has been defined as the presence of some residual superior vermis in the setting of a midline posterior fossa fluid collection that appears to be in communication with the fourth ventricle through a significantly enlarged valleculla, usually with a lesser degree of expansion of the posterior fossa.^{4,5} In DWV, the cerebellar vermian remnant is rotated superoanteriorly. CSF communication between the expanded fourth ventricle and the subarachnoid space is variably present, and hydrocephalus is less common.⁶ A persistent Blake pouch has been more recently defined as a posterior fossa cyst in communication with the fourth ventricle, often through a mildly expanded valleculla. The cyst walls are sometimes visible on sagittal magnetic resonance (MR) imaging as distinct from the subarachnoid space. The inferior vermis is elevated and compressed to a degree, but its anatomical divisions as seen on a sagittal plane MRI are preserved.^{2,3} Lastly, a mega cisterna magna appears as an expansion of the subarachnoid spaces of the posterior fossa. It is distinguished anatomically

from a posterior fossa arachnoid cyst by its free communication with the rest of the subarachnoid space and the fourth ventricle. The cerebellum appears normal or anteriorly displaced, and the valleculla is only minimally or not enlarged. The inferior vermis is not focally compressed as it appears to be in a persistent Blake pouch.⁶ The reader should be aware that considerable disagreement exists regarding the precision of these definitions.⁷

Pathogenesis

The combination of cerebellar dysgenesis, a large posterior fossa cyst, and hydrocephalus was first described by Sutton in 1887.⁸ Walter Dandy and Kenneth Blackfan reported a similar case in their 1914 treatise on CSF physiology.⁹ They observed that the foramina of Luschka and Magendie appeared to be absent. Dandy and others reported case series in which the etiology of the cystic dilatation in the posterior fossa was identified as occlusion of the outflow foramina of the fourth ventricle.^{10,11}

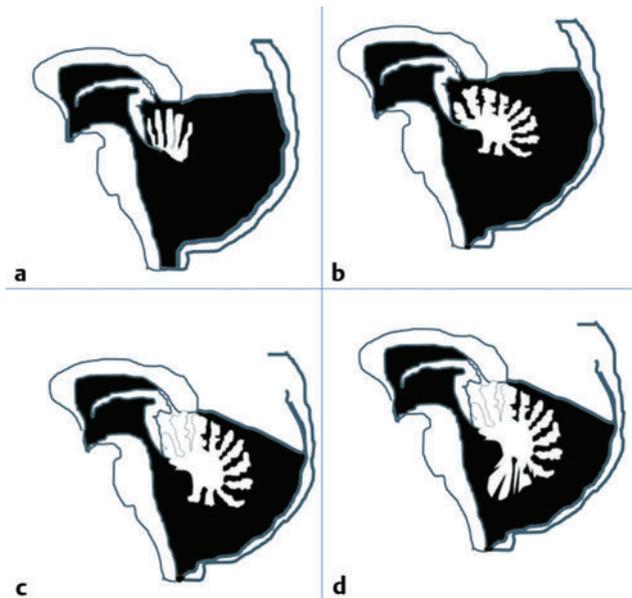


Fig. 13.1 The continuum of the Dandy-Walker complex. (a) Dandy-Walker malformation: posterior fossa enlarged, with minimal to no vermian remnant present and rotated superoanteriorly. Note: The corpus callosum is shown in this diagram for ease of understanding. However, agenesis of this structure frequently coexists with the Dandy-Walker malformation. (b) Dandy-Walker variant: posterior fossa enlarged, superior cerebellar vermis partially preserved and lobulated. (c) Persistent Blake pouch: posterior fossa volume only modestly enlarged, cerebellar vermis fully present and lobulated, inferior vermis compressed, valleculla enlarged. (d) Mega cisterna magna: posterior fossa volume modestly enlarged or normal, cerebellar vermis fully present and lobulated, valleculla normal in size. (Modified from Yildiz H, Yazici Z, Hakyemez B, Erdogan C, Parlak M., Evaluation of CSF flow patterns of posterior fossa cystic malformations using CSF flow MR imaging. *Neuroradiology* 2006;48(9):595-605.)

However, other authors identified similar cases in which the foramina of Luschka and Magendie were patent.¹² As an alternative to the hypothesis of foramina atresia, Benda proposed that maldevelopment of the cerebellar vermis was likely responsible.¹³ Supporting this, Brodal and Hauglie-Hanssen, in their seminal paper, presented two autopsy cases with detailed dissections.¹⁴ The posterior vermis was underdeveloped in both, while the more anterosuperior vermian structures were preserved. The posterior vermian remnant was noted to be continuous with the cyst lining, which had some ependymal features and which they felt was continuous with the rest of the fourth ventricular ependyma. They noted that in the human embryo, the cerebellar anlagen fuse and the vermian divisions form well before the fourth ventricular outflow foramina open. The fusion begins superiorly and proceeds inferiorly. Given the maldevelopment of the vermis seen, they argued that the primary defect must be with the precursor of this structure, the anterior membranous area (AMA).¹⁴ The appeal of this hypothesis is that it appears consistent with the variability of vermian dysgenesis seen across the DWC.

In the developing embryo, the posterior membranous area (PMA) is separated from the AMA by the developing choroid plexus. The PMA normally regresses, with the foramen of Magendie developing in its place. Tortoni-Donati et al, and later Calabrò et al, postulated that the Blake pouch, a small expansion of the PMA seen in utero, can persist and expand rather than regress to give rise to a posterior fossa fluid collection in communication with the fourth ventricle in which the inferior vermis is appropriately lobulated, if compressed.^{2,3,15} It has been further argued that the mega cisterna magna also could be categorized as a PMA developmental abnormality in which the developing PMA cyst eventually becomes connected with the subarachnoid space.^{3,15}

The reader should be aware that considerable controversy exists about whether the radiographic and clinical features occurring in DWM, DWV, and persistent Blake pouch should be considered discrete or continuous. Barkovich et al, noting the variability in radiographic findings, have argued that these entities should be viewed as a continuum.¹⁴ Geneticists and others focused on the various associated malformations seen in various aspects of DWC have argued for a more compartmentalized view.¹⁶

13.1.2 Epidemiology

In a population-based study of members of the Saudi Arabian Armed Forces and their families, DWM had an incidence of 1 in 100,000 live births.¹⁷ Long et al reported another population-based study, from northern England, wherein DWMs and DWVs were identified in utero in 1 per 11,574 live births (approximately 9 per 100,000). Most were identified on prenatal ultrasound, and 47% had associated congenital malformations. Prenatal termination, fetal demise, or neonatal demise occurred in the 43 of 47 prenatally diagnosed cases.¹⁸ Hirsch et al derived an incidence of 3 to 4 per 100,000 live births, calculating this from the incidence of hydrocephalus and the frequency of DWMs in their cohort.¹⁹ Most, although not all, studies show an increased incidence in females.^{18–21} Familial cases of DWM have been reported, but without clear inheritance patterns.^{22–24}

Reefhuis et al, using the National Birth Defects Prevention Study, noted the use of clomiphene citrate to be associated with an increased likelihood of DWMs (adjusted odds ratio [OR], 95%; confidence interval [CI], 4.44, 1.7–11.6) among a variety of other malformations, including congenital heart disease, craniosynostosis, cloacal exstrophy, and omphalocele.²⁵ Prenatal exposures to a number of other agents, including benzodiazepines and coumadin, have been reported in association with DWMs, but without sufficient power to draw conclusions.

A wide variety of genetic abnormalities have been reported in patients with DWM. Chromosome 3, specifically 3q24, which includes two genes encoding for cerebellar formation, has been implicated. Deletions of this region in animal models produce an appearance similar to DWM. Trisomy of chromosomes 9, 13, and 18 has been reported frequently in the genetic analysis of affected individuals.²⁶

13.1.3 Clinical Presentation

In neurosurgical series, the most common presentation is hydrocephalus, with rates of up to 80% of patients with DWM.^{19,20,27,28} In a population of children all with DWV, Sasaki-Adams et al reported a 29% rate of ventriculomegaly, but only 14% of the patients required surgical treatment.²¹ The incidence in nonsurgical series is likely lower. Most children present within the first year or two after birth. In many, the diagnosis is known from prenatal studies. The specifics of the presentation depend on the patient's age; infants present with progressive macrocrania, bulging fontanel, and upward gaze palsy. The speed at which patients become symptomatic is not uniform. In the series of Raimondi et al, children presented between 2 and 9 months of age.²⁹ Hirsch et al reported that 80% presented before 1 year of age, but 7 of 40 required their first treatment after 2 years of age.¹⁹ Additional symptoms may include bilateral nystagmus, alterations in speech cadence, weakness, and respiratory difficulties.²⁹ Opisthotonos has been reported, presumably due to brainstem compression.³⁰ Older patients who survive infancy and can be assessed in more detail often show a striking lack of ataxia relative to the degree of cerebellar malformation. Adult presentation has been reported with both hydrocephalus and cerebellar symptoms.^{31,32} As noted above, the majority of children born with DWMs will have associated abnormalities, which may dictate their clinical presentations. Some patients are asymptomatic and identified incidentally.³³

13.1.4 Associated Conditions

Both CNS and systemic anomalies occur in association with DWC. Depending on the setting of the study and the specifics of the malformation studied, between 50 and 80% of patients are affected. When component diagnoses of DWC are compared, malformations are very common in both DWM and DWV, and it is not yet clear whether DWV has a much lower incidence of such associated malformations, as is sometimes supposed. Has et al reported a prenatal series of 64 fetuses with DWM and 14 with DWV. Because of the setting, 45% of the parents were consanguineous. Excluding hydrocephalus, 23% (DWM) and 42% (DWV) had CNS malformations, most commonly agenesis of the corpus callosum in 10%. Non-CNS abnormalities were present in 44% and 64% of the patients with DWM and DWV,

respectively.³⁴ Sasaki-Adams reported on a group of 24 children with DWV followed over a mean 5 years, with four requiring shunt placement for hydrocephalus. Associated CNS abnormalities included agenesis of the corpus callosum (21%), schizencephaly, seizures, and cortical blindness. Non-CNS malformations were most commonly cardiac (42%) and gastrointestinal (33%).²¹ When diagnoses were made in utero, 56% of the patients with mega cisterna magna in the aforementioned population study from northern England were found to have associated anomalies, although their developmental outcome was dramatically better (25 of 29 were normal) than that for patients in this study with DWM or DWV. Given the midline nature of DWC, it is not surprising that many of the associated abnormalities are also located in the midline, including occipital encephaloceles.¹⁹ The box “Syndromes Associated with the Dandy-Walker Complex” lists a number of other neurologic abnormalities that have been noted.

Syndromes Associated with the Dandy-Walker Complex

- Aase-Smith syndrome
- Beemer-Langer syndrome
- Chondrodystrophia calcificans congenita
- Chronic hereditary polyneuropathy
- Coffin-Siris syndrome
- Cornelia de Lange syndrome
- DiGeorge syndrome
- Down syndrome
- Ellis-van Creveld syndrome
- Facioauriculovertebral syndrome
- Fetal akinesia deformation sequence
- Genoa syndrome
- Goldston syndrome
- Juberg-Hayward syndrome
- Kallmann syndrome
- Klippel-Feil syndrome
- Marden-Walker syndrome
- Meckel-Gruber syndrome
- Neurofibromatosis
- Neurocutaneous melanosis
- Oculocerebrocutaneous syndrome
- Opitz C syndrome
- Oral-facial-digital syndromes
- Partial trisomy 22
- PHACES (posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, sternal defects) syndrome
- Renal-hepatic-pancreatic dysplasia
- Rokitansky syndrome
- Ritscher-Schinzel (3C: cranial vault, cerebellar, cardiac) syndrome
- Sjögren-Larsson syndrome
- Smith-Lemli-Opitz syndrome
- Tetrasomy 9
- Trisomy 9
- Turner syndrome
- Walker-Warburg syndrome
- Yunis-Varon syndrome

DWC has been seen in a wide variety of named syndromes, which are listed above. Most of these appear in isolated case reports, but several appear with more regularity, including PHACES syndrome (posterior fossa abnormalities, hemangioma of the face, arterial abnormalities, coarctation of the aorta, eye abnormalities, sternal defects)^{35,36} Ritscher-Schinzel (3C) syndrome (cranial vault, cerebellar, cardiac)³⁷ neurocutaneous melanosis³⁸ and Meckel-Gruber syndrome (renal cystic dysplasia, CNS malformations, polydactyly, hepatic defects, pulmonary hypoplasia). In the latter, a Dandy-Walker cyst can replace the more common occipital encephalocele.^{39,40} Source: From Raimondi AJ, Sato K, Shimoki T. The Dandy-Walker Syndrome. Basel, Switzerland: S Karger; 1984:21–45, as presented in Wilkinson C, Winston K. Congenital arachnoid cysts and the Dandy-Walker complex. In: Albright AL, Pollack IF, Adelson PD, eds. Principles and Practice of Pediatric Neurosurgery. 2nd ed. New York, NY: Thieme Medical Publishers; 2007:165.¹⁸⁴

13.1.5 Radiology and Treatment Planning

Radiographic findings in DWC mirror the anatomical details already noted. The enlarged posterior fossa and thinned cranium can be seen on plain skull radiographs. In the normal individual, the torcular herophili lies below the lambda on skull X-rays. The vascular grooves created by the sinuses are seen below the lambdoid sutures. Lambdoid-torcular inversion occurs with the expansion of the posterior fossa seen in DWC, such that the confluence of the sinuses can lie above the lambda and is seen above the lambdoid sutures on plain X-ray. Angiographically, in the arterial phase, the posterior inferior cerebellar arteries may be absent.⁴¹ In the venous phase, the oblique course of the transverse sinuses and upward course of the straight sinus are noted.²⁹

The accuracy of prenatal ultrasound for the diagnosis of DWM/DWV has ranged in the literature from as low as 40% to up to 92%.^{18,42} Diagnosis before 18 weeks of age may have a higher error rate.¹⁸ Fetal MR imaging is increasingly being performed. Although MR imaging has significant advantages postnatally, the accuracy of prenatal diagnosis in early gestation has been questioned. Patek et al reported on 59 fetuses found on MR imaging to have posterior fossa abnormalities demonstrating the spectrum of findings seen in DWC. When the patients were assessed on postnatal imaging, for those with findings equivalent to DWV, the sensitivity was 50% (5 of 10) when the study was performed before 24 weeks, compared with 100% (9 of 9) when MR imaging was performed after 24 weeks.⁴³ Postnatally, however, MR imaging is clearly the diagnostic study of choice, revealing the posterior fossa anatomy considerably better than ultrasonography, and MR imaging is more sensitive to other CNS abnormalities seen, such as those listed in the box “Syndromes Associated with the Dandy-Walker Complex.”

When the treatment of patients with DWC is being planned, knowing which of the various fluid spaces are in communication may be helpful. The aqueduct of Sylvius may appear obviously occluded on standard MR images. However, CT after contrast injection into the ventricular system or cyst may be a more definitive study, although at the cost of radiation

exposure, usually in a young patient. As an alternative, phase-contrast MR imaging has been proposed to determine the relative patency of the cystic structures in DWC. Yildiz et al reported a very high correlation rate between phase-contrast cine MR imaging and CT cisternography in delineating the anatomy of the DWC variations and in differentiating between these and posterior fossa arachnoid cysts.⁶

13.1.6 Treatment

DWC spans a variety of clinical presentations and therefore treatment needs. DWM is associated with hydrocephalus in 80% of cases, so most patients with DWM become symptomatic and require treatment at some point in early childhood. Surgical options include CSF shunt placement, endoscopic management, and open surgical treatment. Because of the high morbidity associated with early open surgical treatments, CSF shunt placement became the principal treatment as soon as shunts were readily available.^{29,44}

The debate about whether a CSF shunt should be placed into the ventricular system, the cyst, or both has been continuing since the onset of shunt treatment and remains unresolved, save for agreement that placing the catheter into one of the spaces necessitates either preoperative demonstration of communication between the spaces or careful postoperative observation for evidence of loculation formation and noncommunication. Supporting treatment of just one compartment, Mohanty et al noted that 23 of 26 patients with DWM in their series had a patent aqueduct on MR imaging.⁴⁵ Hirsch et al reported success with isolated shunt systems in either compartment.¹⁹ However, Asai et al, reporting the Toronto Hospital for Sick Children series of 35 patients, noted that 9 of 21 patients (43%) treated with isolated ventricular shunts developed noncommunication with the cyst, necessitating cyst shunt treatment.⁴⁶ Osenbach and Menezes reported that 75% of patients with DWM had noncommunication requiring shunting of both compartments.²⁸ Naidich et al identified radiographic findings of downward herniation of the supratentorial contents after cyst decompression or lateral ventricular shunt obstruction in 25 patients with DWM.⁴⁷ Kumar et al reported that 9 of 28 patients (32%) treated with ventricular shunts required subsequent cyst shunts, compared with 6 of 7 patients (86%) with a cyst shunt who later required ventricular shunts.²⁷ Mohanty et al reported that 12 of 24 cyst shunts failed, compared with 4 of 21 ventricular shunts. Five patients went on to require shunting of both compartments, and endoscopic techniques were also used.⁴⁵ Those advocating shunt placement in both compartments have generally argued for a two-limbed shunt so that both the posterior fossa and supratentorial space are exposed to the same intracranial pressure (ICP).²⁹

A number of surgical pitfalls must be avoided during CSF shunt placement in this population. If a cyst catheter is to be placed, a lack of brain parenchyma to pass the catheter through increases the incidence of postoperative CSF leak or subcutaneous collection, with this occurring in 29% of patients with cyst shunts in one case series.⁴⁵ A very small durotomy for catheter placement, appropriately compressive dressings, and potentially an adjustable-pressure valve with a low initial setting may help limit the potential for this

complication. The enlarged posterior fossa in DWM means that the standard external landmarks for posterior ventricular shunt placement are unreliable. In addition, the dural venous anatomy is distorted, and there is risk that a bur hole intended for a supratentorial catheter may be placed over the transverse sinus. Intraoperative ultrasound can be a valuable adjunct in patients with open fontanelles to guide catheter placement. Simultaneous single-catheter placement into both the ventricular and cystic cavities has been reported with ultrasound guidance.⁴⁸ More recently, the neuroendoscopically assisted cannulation of ventricular and cyst cavities with a single catheter has been advocated.^{49,50}

Shunt failure is reported in all surgical series. In the above-cited case series, the shunt failure rates range from 4 to 60% over variable follow-up. If one compares these rates with those in similarly structured case series for other types of hydrocephalus, the results are not clearly different. Other complications include brainstem or cranial nerve injury from catheter placement, intracystic hemorrhage, and catheter migration into or out of the posterior fossa cyst.^{51,52} Chronic traction on the brainstem from a cyst catheter adherent to it, with neurologic injury, has been reported.⁵³

Endoscopic third ventriculostomy (ETV) in patients with DWM has been reported as part of larger series.^{45,54,55} Given that some patients have patent aqueducts, and assuming obstruction at the outflow of the fourth ventricle or cyst, this should be a reasonable choice. Distortion of the third ventricle and a narrow prepontine subarachnoid space increase the complexity of such procedures, but success has been reported in what would otherwise appear to be challenging cases.⁵⁶ In cases of noncommunication between the ventricles and DWM, endoscopic cyst fenestration to the ventricular system has been advocated as an addition to ETV. Mohanty et al used endoscopic techniques in addition to CSF shunt placement in 21 patients, with 5 failures (23%) requiring alternative procedures. The authors describe ETV, cyst fenestration, and guided stent placement through the superior vermian remnant from the supratentorial space.^{45,57} Warf et al reported on their experience in Uganda treating DWM/DWV with ETV and choroid plexus coagulation in 45 children who had a mean age of 5 months at treatment. With a minimum of 6 months' follow-up (mean, 24 months), 74% of the patients had not required an additional procedure. The authors observed that 39 of 41 patients had an open aqueduct as seen endoscopically at surgery.⁵⁸

Direct surgical resection of the cyst wall was the initial procedure performed before the availability of CSF shunts. It had a high failure rate and a high associated mortality rate. Summarizing nine case series reported between 1947 and 1984, Hirsch et al noted a 75% failure rate and 10% surgical mortality rate.¹⁹ However, a number of more recent publications detail, albeit in small numbers of patients, less adverse outcomes with open techniques than those in older reports.^{59,60}

13.1.7 Outcome

Survival

The analysis of outcomes for patients with DWC is complicated by the variability of the complex itself and the associated

malformations. In addition, selection and survivor biases are clearly complicating factors in addressing this question. Using the Congenital Malformations Registry of the New York State Department of Health, Salihu et al reported a 25% mortality rate by the end of the first year of life in 196 cases. The death rates were 16% for patients with isolated DWS, 32% for those with DWS and one additional organ system anomaly, and 42% for those with involvement of two or more additional organ systems.⁶¹

Intellectual Outcome

Neurodevelopmental outcomes are similarly variable. Among long-term survivors from before 1984, Hirsch et al reported that 49% had IQ scores above 90.¹⁹ A number of authors report a relationship between the degree of cerebellar dysgenesis and intellectual outcome. Gerszten and Albright reported that 45% of 120 patients with DWS had normal intelligence. Using CT images to measure the ratio of cerebellar volume to posterior fossa volume, they noted no relationship between the ratio and intellectual outcome.⁶² However, using MR imaging, Boddaert et al reported that in 21 children with DWC, those with normal cerebellar lobulation had an 82% rate of normal intelligence, whereas no child with abnormal cerebellar lobulation had normal intelligence.⁶³ Klein et al also reported a much more favorable intellectual outcome with only partial as opposed to severe vermian abnormalities.⁶⁴

With specific reference to DWV, developmental outcomes have generally been assumed to be better than those in DWM, but as in DWM, a wide range of outcomes is reported, and associated congenital anomalies appear to play a major role. Sasaki-Adams noted that 5 of 6 patients with isolated DWV had normal development, but 10 of 15 with DWV and associated abnormalities were impaired, 6 of them severely.²¹ Mega cisterna magna is generally thought of as a benign condition, and neurodevelopmental assessments in such patients support this view, with the exception that, as in other DWC entities, associated abnormalities play a significant role.^{43,65}

13.2 Arachnoid Cysts

Intracranial arachnoid cysts are arachnoid-lined expansions of the normal subarachnoid and, in some cases, intraventricular spaces. They are more common in boys than in girls, more often left-sided than right-sided, and more often above the tentorium than below it. Common sites include the middle cranial fossa, the suprasellar region, the quadrigeminal plate region, and the posterior fossa. Arachnoid cysts are usually asymptomatic, but they occasionally cause symptoms and require treatment. Treatment options include craniotomy for microsurgical cyst fenestration, endoscopic fenestration, and CSF shunt placement. The indications for treating an arachnoid cyst must be carefully considered in light of the natural history of these lesions.

13.2.1 Pathogenesis

The first clear description of an intracranial arachnoid cyst is usually credited to Richard Bright in *Reports of Medical Cases*, published in 1831. Bright identified the intra-arachnoidal location of the fluid collection and the variable size of cysts found

in different individuals. He also noted the remodeling of the brain and bone caused by the cyst. He identified most of these cysts as likely chronic, with little propensity for change.^{66,67} A variety of explanations for the origin of the arachnoid cyst have subsequently been proposed, including posttraumatic and infectious etiologies.^{68–70} Most cysts, however, likely have a congenital origin, particularly those diagnosed in childhood. Microscopically, the cyst appears as a duplicated layer of otherwise normal arachnoidal tissue that forms the cyst wall.^{68,71} In their ultrastructural study, Rengachary and Watanabe identified a split in the arachnoid membrane at the margin of the cyst, associated thickening of the collagen in the arachnoid cyst wall, hyperplasia of arachnoid cells in the cyst, and the absence of the typical spiderlike processes that define the normal arachnoid membrane. They postulated that the cysts develop in utero.⁷² The exact timing of cyst development in utero is uncertain. Studies of associated developmental venous anatomy suggest that cysts in the sylvian fissure may form in the middle of the first trimester.⁷³ Prenatal imaging has similarly demonstrated arachnoid cysts as early as the first trimester.⁷⁴ Bannister et al reported on 15 fetuses in a single-institution review. Five were diagnosed before 20 weeks. Thirteen cysts were supratentorial.⁷⁵ The authors noted that ultrasound diagnosis was sometimes difficult, with two of four aborted fetuses in this series having other etiologies accounting for the ultrasound findings. Arachnoid cysts have also been evaluated with fetal MR imaging.^{76–78} Case series of children with prenatally diagnosed arachnoid cysts report a higher incidence of associated abnormalities and the need for surgical treatment than do series of children with a postnatal diagnosis.^{75,76}

From a developmental standpoint, the predominance of a middle fossa location, the left-sided predominance, and the male predominance seen in intracranial arachnoid cysts lack a proven explanation. Wester conjectured that during the anterior growth of the temporal lobe adjacent to the frontal tissues, which creates the sylvian fissure, the leptomeningeal tissues are carried along with the cerebral lobes, so that the temporal and frontal arachnoid tissues are placed in apposition. If the developing frontal and temporal arachnoid tissues fail to fuse, cyst formation can then occur.⁷⁹ However, cysts in other locations cannot be readily explained by a similar mechanism. No clear hypothesis for the male predominance or left-sided predominance has been advanced.

Fox and Al-Mefty proposed that suprasellar arachnoid cysts form from an upward diverticulum of the membrane of Lilliequist.⁸⁰ Open or endoscopic surgical treatment of these lesions frequently discloses a much more thickened and tough membrane than is seen in middle fossa arachnoid cysts. Rests of arachnoidal tissues are periodically present in the ventricular system and are thought to account for the rare intraventricular meningioma. These cells are presumably also the source of the equally rare intraventricular arachnoid cyst.

Three theories have been advanced for how fluid accumulates in an arachnoid cyst. First, based on surgical observation, arachnoid tissues have been seen to form a one-way valve, admitting fluid during one phase of the cardiac cycle but not allowing it to subsequently escape. Second, cyst fluid may accumulate as the result of an osmotic gradient. Third, the arachnoid membranes may actively secrete the cyst contents. Schroeder and Gaab provide endoscopically acquired photographs of a slit valve in the

base of a suprasellar arachnoid cyst.^{81,82} Similar findings have been noted on cine MR imaging.⁸³ The contents of an arachnoid cyst are typically thought of as being identical to spinal fluid. However, increased cyst protein concentrations were noted in a group of 54 pediatric patients undergoing open surgical treatment.⁸⁴ The authors argued that this supported an osmotic mechanism. However, the patients did not act as their own comparators for the study, with reference CSF values being used instead. Berle et al, conversely, provided an analysis of fluid drawn from both the subarachnoid space and the arachnoid cyst in 15 patients undergoing surgical treatment. Although most electrolyte concentrations were similar, increased concentrations of phosphate, along with decreased concentrations of protein, ferritin, and lactate dehydrogenase, were noted in the cyst fluid. The authors argued that a ball-valve mechanism for filling would not allow these differences. Fluid osmolarity was similar, arguing against an osmotic force. The authors interpreted these data as supporting fluid secretion by the cyst walls or some other active transport mechanism.⁸⁵⁻⁸⁷ Earlier studies had also suggested an active transport mechanism in cyst fluid formation.⁸⁸ It is of course possible that several mechanisms may be in operation.

Trapped fluid within the arachnoid cyst displaces and distorts the adjacent neural and neurovascular structures. The degree to which neural structures tolerate the sometimes significant displacement is remarkable.⁸⁹ Even very large cysts with significant brain displacement are regularly found incidentally, particularly in the middle and anterior cranial fossae. Conversely, large midline cysts, particularly in the suprasellar region, frequently produce endocrine dysfunction and hydrocephalus.⁹⁰⁻⁹² Quadrigeminal plate arachnoid cysts are frequently associated with hydrocephalus. A variety of functional studies have addressed whether large supratentorial arachnoid cysts distort normal cerebral metabolism, with conflicting results. Wester and Hugdahl reported changes in measures of verbal laterality and handedness following surgical decompression of left temporal and frontal arachnoid cysts, with abnormal test values returning to those seen in a normal reference group after surgery.⁹³ Hund-Georgiadis et al used functional MR imaging to study language dominance and regional temporal anatomy in five right-handed patients with large left-sided arachnoid cysts. Four were left-dominant for language, despite the large ipsilat-

eral cysts, and the fifth showed mixed dominance.⁹⁴ Positron emission tomography (PET) studies in a similar group of four right-handed patients with left-sided cysts showed no right-sided language activity. However, PET/CT studies in a 51-year-old with a very large right frontal arachnoid cyst demonstrated normal cortical metabolism adjacent to the cyst, but the right cortical motor pathways were reorganized.⁸⁹ Single-photon emission computed tomography (SPECT) studies of three children with middle fossa arachnoid cysts demonstrated both local and contralateral perfusion defects that resolved after surgical intervention.⁹⁵ SPECT and cognitive improvement after surgical cyst treatment has also been reported.⁹⁶

Nonneurologic consequences of cysts have also been reported. Pressure from a cyst may thin the bone adjacent to it, rarely even to the point of incompetence, with CSF leaks occurring to the middle ear,⁹⁷ scalp⁹⁸ and nasal cavity.⁹⁹⁻¹⁰¹

13.2.2 Incidence and Epidemiology

After a review of nearly 12,000 pediatric MR imaging studies at a single institution, Al-Holou et al reported the MR imaging incidence of arachnoid cysts in children to be 2.6%. The male incidence was 3.8%, versus 1.8% for the female incidence. This male predominance persisted throughout all pediatric age ranges.¹⁰² Males also had statistically larger cysts than females on average. There was no increase in the incidence throughout childhood—that is, new cases were not detected more commonly at older ages. Middle fossa cysts accounted for 45% of all cysts and were twice as common on the left side as on the right. About one-third of cysts were located in the posterior fossa, with the majority posterior to the cerebellum and 6% in the cerebello-pontine angle (► Fig. 13.2).¹⁰² Contrasting with the findings in earlier, smaller studies, there was no gender difference between cyst sidedness.^{79,103} Earlier estimates in the literature, also from smaller samples, noted incidence rates from 0.3 to 1.7%, with the study patients mostly adults.¹⁰⁴⁻¹⁰⁶ Most incidence studies have similarly identified an increased incidence of cysts in males and a left-sided predominance, particularly for middle fossa arachnoid cysts. Using the same methodology as in the aforementioned pediatric study, Al-Holou et al reported a 1.4% adult incidence of arachnoid cysts drawn from a database of more than 48,000 MR imaging studies, with a male

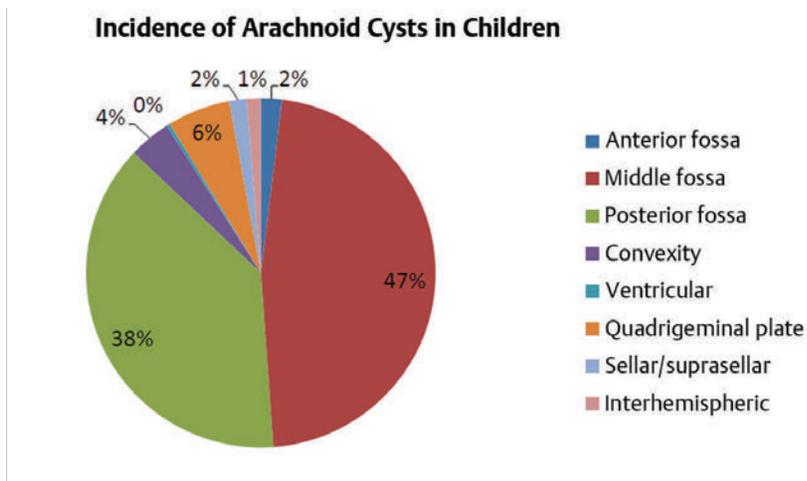


Fig. 13.2 The incidence of arachnoid cysts in 309 children drawn from a sample of 11,738 consecutive MR imaging studies. (Modified from Al-Holou WN, Yew AY, Boomsaad ZE, Garton HJ, Muraszko KM, Maher CO. Prevalence and natural history of arachnoid cysts in children. *J Neurosurg Pediatr* 2010;5 (6):578-585.)

predominance (1.8% vs. 1.1%) There was no change in incidence by age. Middle fossa cysts (34%) and retrocerebellar cysts (17%) were seen most commonly.⁹⁰

Arachnoid cysts have also been reported in multiple other sites, including within the sella turcica,^{107,108} within the ventricular system¹⁰⁸⁻¹¹⁰ and between the cerebral hemispheres.¹¹¹ Suprasellar, quadrigeminal plate, ambient cistern, cerebellopontine, and retrocerebellar arachnoid cysts are also seen.

Middle fossa cysts have been classified by Galassi et al.¹¹² Type 1 cysts are small and lens-shaped, are located at the proximal sylvian fissure, and do not produce any midline shift. Galassi et al reported that these cysts appear to fill with spinally injected contrast media. Type 2 cysts are more rectangular in shape and extend in the sylvian fissure to border the insula. Minimal midline shift may be present. Type 3 lesions involve the entire sylvian fissure, with thinning of the adjacent bone and more obvious midline shift, and they do not appear to communicate with the subarachnoid space on contrast injection. Of the middle fossa cysts in children reported by Al-Holou et al, 68% were type 1, 15% were type 2, and 17% were type 3.¹⁰² In most case series, type 1 lesions are less likely to be treated than type 2 or 3 lesions.

No clear ethnic or racial trends have been reported for arachnoid cysts. Familial occurrence has been reported.¹¹³ Arachnoid cysts have been associated with a myriad of conditions in case reports, but given their relatively common occurrence, these associations are more likely to be coincident than causal. However, two conditions are more firmly linked to arachnoid cysts. Autosomal-dominant polycystic kidney disease (ADPKD) is associated with an increased incidence of arachnoid cysts. Schievink et al reported an 8.1% incidence of arachnoid cysts in a group of 247 patients with ADPKD. There was also a higher incidence of cystic liver disease in the patients with ADPKD and arachnoid cysts than in those without. However, no patient in this series required treatment for an arachnoid cyst.¹¹⁴ Additionally, glutaric aciduria type 1 is associated with bilateral middle fossa arachnoid cysts. Patients with this disorder may be at increased risk for harm during surgical procedures.¹¹⁵⁻¹¹⁸

13.2.3 Natural History

Size

Most arachnoid cysts do not expand after initial radiographic diagnosis. In a study of 111 pediatric patients with a mean follow-up of 3.5 years and serial MR imaging, 87 cysts remained stable in size, 11 increased in size, and 13 decreased in size. Only 3 patients in this series became symptomatic. All patients whose cysts expanded were less than 4 years of age at initial diagnosis, and follow-up was similar for those younger and older than 4 years.¹⁰² Among adult patients studied by the same group, of 213 cysts followed over a mean of 3.3 years, 5 (2.3%) increased in size, while 2 (1%) decreased in size.⁹⁰ A number of other studies have identified the connection between young age at diagnosis and the possibility of cyst expansion. Rao et al reported 2 children, 4 years of age or younger, who developed symptomatic expansion. In reviewing the pediatric literature to 2005, they identified 3 additional cases of radiographically documented symptomatic expansion in children who, they reported, were ages 8 months, 7 years, and 6 months.^{119,120} Radiographic resolution has also been documented on follow-up imaging.¹²¹⁻¹²³

Intracystic Hemorrhage and Subdural Hygroma

Rarely, arachnoid cysts may rupture and present with a subdural CSF fluid collection. This is often associated with either modest or more dramatic subdural hemorrhage, presumably from the tearing of bridging veins associated with the cyst wall. Rupture has been reported to occur both after trauma and spontaneously.¹²⁴⁻¹²⁶ Radiographic resolution has been reported after rupture¹²⁷ and has been seen in the author's practice even without surgical intervention. Cress et al reported hemorrhage in 14 of 232 patients (6%) identified through an imaging database at a single institution. Using a case-control methodology, matching the patients for age, sex, side, and anatomical location with patients who had unruptured arachnoid cysts, the authors noted that children with rupture at presentation were more likely to have symptoms of intracranial hypertension and to have midline shift associated with their cysts. Cyst size larger than 5 cm in any dimension and prior head injury within 30 days were seen with statistically much greater frequency in the cohort with rupture, but altitude of residence was not different. Of the 14 patients with rupture, 10 were managed surgically. All patients recovered fully, but 14% required permanent CSF shunt placement.¹²⁸ Other studies have reported a lower incidence of hemorrhage. Al-Holou et al reported 1 patient presenting with hemorrhage among 309 children (0.3%) with arachnoid cysts identified on MR imaging.¹⁰² Wester and Heland reported 11 of 246 adult and pediatric patients (4.6%) presenting with hemorrhage. All 11 patients underwent surgical treatment and recovered without postoperative morbidity. In this later study, cyst size was not noted to be a risk factor.¹²⁹ Parsch et al, in a largely adult series, noted that 2 of 96 incidentally identified arachnoid cysts drawn from 11,487 imaged patients presented with hemorrhage.¹³⁰

13.2.4 Clinical Presentation

Many arachnoid cysts are diagnosed incidentally when MR imaging is performed for an indication likely to be unrelated to their presence. In the University of Michigan pediatric series, only 6.8% of patients with radiographically identified arachnoid cysts were felt to be symptomatic.¹⁰² However, among the patients deemed symptomatic, the clinical manifestations related either to generalized increased ICP or to focal symptoms resulting from displacement or compression of specific structures by the arachnoid cyst. In symptomatic infants, there is often associated hydrocephalus, and the presentation of progressive macrocephaly, split sutures, and a Parinaud syndrome can occur. In older children, headaches, nausea and vomiting, lethargy, sixth nerve palsy, and papilledema can all occur. In the middle fossa, a cyst can cause focal prominence of the overlying bone and distortion of the adjacent orbit with proptosis. Suprasellar arachnoid cysts can produce endocrinopathy related to deformity of the pituitary axis and visual disturbance from displacement of the optic apparatus. Quadrigeminal plate arachnoid cysts most frequently produce hydrocephalus but may cause a Parinaud syndrome from local deformation of the tectum. Cerebellopontine angle cysts have been associated with nystagmus, facial weakness, hearing loss, and tinnitus.¹³¹ Given the above descriptions, the clinician is faced with the task of determining,

for an individual patient, whether there is a causal relationship between reported complaints and the identified cyst. Information regarding the sensitivity and specificity of common features obtained from the history and physical examination for predicting the potential for future harm or a positive response to treatment is not widely available. This is especially true for common protean symptoms like headache.

Headaches

In most pediatric series of symptomatic patients, headaches are among the most common presenting symptoms.^{102,132-138} The headaches that are associated with arachnoid cysts in the absence of overt hydrocephalus have not been specifically characterized in the literature. Unlike in other neurosurgical conditions, such as Chiari 1 malformation, in which there appears to be a correlation between the specifics of the headache and the likelihood of response to surgical therapy, no similar specificity has been demonstrated for arachnoid cysts. One can speculate that the pain arises from dural compression or displacement of the dura, given its rich sensory innervation, although focal episodic pain is more likely to be migrainous in an otherwise neurologically normal child. However, why some patients with cysts that cause mass effect on adjacent bone or midline shift have headaches and others do not is not known. One study has looked at the relationship between intracranial hypertension, cyst size, and clinical symptoms. Di Rocco et al reported on 11 children with middle fossa arachnoid cysts who underwent ICP monitoring. The ICP was observed to be normal (< 10 mm Hg, author's definition) in 3 children with smaller, Galassi type 1 cysts, although 2 of these 3 had headaches. Of 7 patients who had larger, Galassi type 2 cysts, none had headaches. Half of these children had ICPs more consistently about 10 mm Hg, half had ICPs below. Two patients with larger, type 3 cysts had significant ICP elevations, one with headache.¹³⁹ Migraine headaches in children are common, with a prevalence of 2.7 to 10.6%¹⁴⁰ Given that arachnoid cysts are also relatively common, a significant number of children will present with both entities as a matter of chance.

Epilepsy

In surgical series, seizures occur in 20 to 34% of patients with arachnoid cysts.^{132,134,136} However, this is almost certainly a selection bias, because the incidence in nonsurgical series is considerably lower. In the previously noted MR imaging study of the incidence of arachnoid cysts, Al-Holou et al reported that there was a concern for seizures in 16% of children undergoing MR imaging studies in whom an arachnoid cyst was present.¹⁰² Presumably, the actual incidence of epilepsy was lower. The relationship between arachnoid cysts and seizures is not straightforward. Although one might postulate a global effect of an arachnoid cyst, increasing the propensity for epilepsy, it is more likely that the effect of the cyst would be felt most on the adjacent tissue. A majority of arachnoid cysts present in the temporal fossa. The temporal lobe is more prone to epilepsy than other regions of the brain. So it might be expected that complex partial epilepsy would be the most common type in patients with arachnoid cysts. Arroyo and Santamaria identified a 2% incidence of arachnoid cysts in a clinic for adults with refractory

epilepsy. However, only 3 of 12 patients with middle fossa cysts had temporal lobe epilepsy. Interestingly, about 25% of the patients with arachnoid cysts in this series were found to have cortical dysplasias remote from the arachnoid cyst.¹⁴¹ Similarly, Yalçın reported seizure diagnoses in 21 patients with arachnoid cysts, mostly in the middle fossa, drawn from a clinical population of 612. Eleven patients had generalized seizures, and 5 had focal nontemporal epilepsy. Four patients had temporal complex partial events, but of these, only one had an ipsilateral cyst.¹⁴² Arai et al assessed with preoperative electroencephalography (EEG) 77 patients with middle fossa arachnoid cysts, who were subsequently treated with cyst-peritoneal shunt placement; 54% had EEG abnormalities and 34% had documented seizures, of whom 16 had generalized seizures, 8 had simple partial seizures, and 2 had complex partial seizures. After shunt treatment with a high rate of cyst decompression, 71% of the observed postoperative EEGs were either unchanged or worse. Of 26 patients, 21 required ongoing medical therapy for seizures, 1 had resolution of the epilepsy, and 4 required significant additional medications or alternative surgery or died as a result of their epilepsy.¹³³ Conversely, multiple surgical series, reviewed below, do show considerable improvements in seizure outcomes, more strongly implying a causal connection.

Developmental Delay and Cognitive Deficits

Surgical series report cognitive disorders and developmental delay in up to a 25% of patients undergoing treatment.¹³² In some cases, these are believed to be due to the arachnoid cyst.¹⁴³ As noted previously, pediatric patients with arachnoid cysts have been demonstrated to have abnormal SPECT studies^{95,144} and PET/CT studies in the brain adjacent to the arachnoid cyst.¹⁴⁵ Neuropsychometric testing in 55 adults conducted pre- and postoperatively and compared with testing in a group of healthy volunteers demonstrated both significantly worse performance at baseline and postoperative improvement in measures of visual retention and of attention and interference, among other parameters tested.¹⁴⁶ Similar improvements in verbal memory in adult patients after cyst decompression have been reported by the same group.¹⁴⁷ However, pediatric case series consistently report little improvement in cognitive delay in patients undergoing cyst decompression, even when other symptoms, such as ICP-related headaches and progressive macrocephaly, are improved.^{133,134}

Suprasellar Cysts and Neuroendocrinologic Disturbances

Suprasellar cysts and large middle fossa cysts that encroach on the hypothalamic-pituitary axis unsurprisingly can produce significant endocrinologic disturbances. Central precocious puberty, inadequate growth hormone production, hypothyroidism, amenorrhea, low plasma testosterone, diabetes insipidus, and the syndrome of inappropriate antidiuretic hormone secretion have all been reported.^{91,92,148,149} Endocrinopathy is frequent enough in patients with suprasellar cysts to recommend screening for all such patients.

The bobble-head doll syndrome, a movement disorder characterized by head bobbing in both the sagittal and coronal planes, usually at a frequency of 2 to 3 Hz, is associated with

lesions of the hypothalamus and third ventricle. It has also been reported with suprasellar arachnoid cysts.^{150–152} In these case reports, cyst treatment is associated with resolution of the symptoms. El-Ghandour, reporting a case series of 25 children with suprasellar arachnoid cysts, noted that all had hydrocephalus, 5 had developmental delay, 1 had visual impairment, and 1 had precocious puberty. Two patients had the aforementioned bobble-head doll syndrome.¹⁵¹

Intrasellar arachnoid cysts have also been reported but are rarely diagnosed in children.¹⁵³

Cerebellopontine Angle Cysts

Cerebellopontine angle arachnoid cysts account for about 15% of all cysts identified in children.^{90,138} In adult patients, cerebellopontine angle cysts are more likely to be symptomatic than arachnoid cysts generally, but this is not clearly so in children.^{90,102} Symptoms reported in children include headaches, vomiting, facial weakness, hearing loss, tinnitus, and ataxia.¹³¹

13.2.5 Radiology

CT and particularly MR imaging are the principal radiographic tools for diagnosis. Although MR imaging is likely the more useful, CT studies can still play an important role in sorting through the differential diagnoses of arachnoid cysts in certain locations and can be an important tool in identifying the rare coincident intracystic or subdural hemorrhage. On CT, cysts without hemorrhage should be identical in density to CSF. MR imaging sequences also can help to demonstrate subdural hematoma in arachnoid cysts.¹⁵⁴ A pitfall is that fat is similar enough in intensity to CSF on CT scans that certain lesions, such as cerebellopontine angle dermoid or epidermoid cysts, cannot be readily distinguished. For this latter diagnosis, even standard T1- and T2-weighted MR imaging may not be helpful. Diffusion-weighted images, however, readily differentiate the hyperintense dermoid cyst from the hypointense arachnoid cyst and should be part of the evaluation of intracranial cystic lesions.¹⁵⁵ Conversely, CT can be very helpful in identifying calcium in suprasellar lesions, which is sometimes hard to discern on MR imaging sequences. Calcium in a cyst wall makes it much more likely for a lesion to be a craniopharyngioma than a suprasellar arachnoid cyst.

With the exception of cysts in the intraventricular location, MR imaging studies should demonstrate that the arachnoid cyst is extra-axial. Particularly, there should be a gray matter boundary to the cyst on the brain side. The author has cared for a child referred with the diagnosis of an expanding arachnoid cyst. On inspection, the lesion proved to have a white matter boundary and was instead an expanding tumor cyst. ▶ Table 13.1 lists entities in the radiographic differential diagnosis by anatomical location.

Suprasellar arachnoid cysts frequently produce hydrocephalus via obstruction at the level of the foramen of Monro. The third ventricle is compressed and displaced posteriorly. However, because the cyst itself is of CSF intensity, on axial imaging, particularly with CT, it can be mistaken for the third ventricle, leading to a mistaken impression of an aqueductal obstruction. In axial imaging, the foramen of Monro is

Table 13.1 Radiographic differential diagnosis of arachnoid cysts by location

Middle, anterior cranial fossa	Porencephalic cyst Epidermoid cyst Loculate subdural hygroma Schizencephaly Neurocysticercosis Cystic neoplasm Choroid fissure cyst Vascular lesion/aneurysm
Sellar and suprasellar	Craniopharyngioma, other cystic tumors, Rathke cleft cyst Dermoid cyst
Midline posterior fossa	Dandy-Walker complex (malformation/ variant/persistent Blake pouch) Mega cisterna magna Neurenteric cyst
Quadrigenial plate region	Pineal cyst Tumor cyst Neuroepithelial cyst
Cerebellopontine angle	Epidermoid cyst Cystic cerebellopontine angle tumor Infectious cyst (should be intra-axial)
Intraventricular	Choroid plexus cyst Ependymal cyst Colloid cyst Neurocysticercosis

Source: Modified from Osborn AG, Preece MT. Intracranial cysts: radiologic-pathologic correlation and imaging approach. *Radiology* 2006;239(3):650–664.¹⁸⁵

typically bowed anterolaterally by the expanding extra-axial suprasellar arachnoid cyst. Sagittal plain imaging is usually diagnostic (▶ Fig. 13.3).

CT cisternography can demonstrate the relative communication of arachnoid cysts with the remainder of the subarachnoid space. The Galassi classification is in part defined by the penetration of subarachnoid contrast.¹¹² However, in practice, cisternography is not commonly used in supratentorial lesions. Conversely, differentiating posterior fossa cystic lesions can be very challenging. The reader is referred to the prior section on DWC. Here, CT cisternography may play an important role. However, more recently, phase-contrast MR imaging has been reported to differentiate CSF communication in both posterior fossa and supratentorial arachnoid cysts.^{6,156}

As noted previously, arachnoid cysts are a common incidental lesion. Once they are diagnosed, there may be a desire for further radiographic follow-up. Cysts can expand; however, as has been discussed earlier, among asymptomatic patients more than 4 years of age, this appears to be uncommon.¹⁰²

13.2.6 Treatment

Indications

Because arachnoid cysts are common, with the finding incidental and many of the symptoms protean, very careful patient selection is warranted to avoid overtreatment. Small, asymptomatic cysts can readily be observed and, in older patients, may

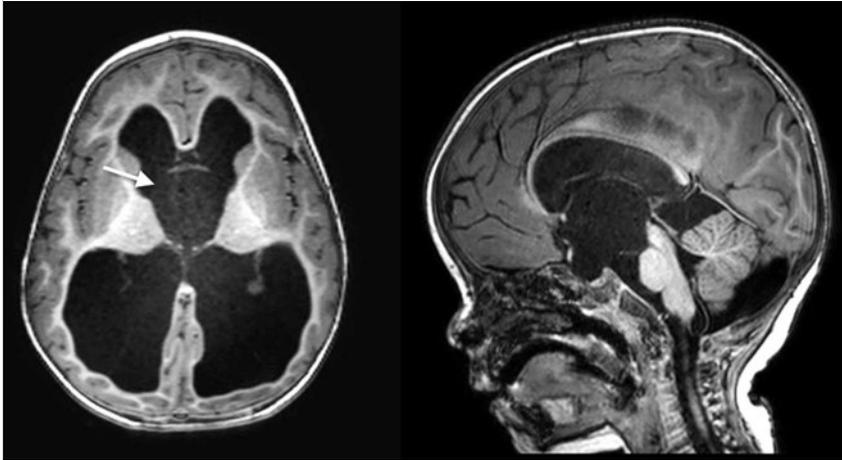


Fig. 13.3 Suprasellar arachnoid cyst. Note the convex appearance of the region of the foramen of Monro.

not require even follow-up imaging. Conversely, patients with clear symptoms of increased ICP that correlate with cyst expansion, such as progressive macrocephaly, papilledema, and progressive cranial neuropathy, are candidates for surgical intervention. A third group with more equivocal symptoms presents the most difficulty. This group includes patients with larger cysts and chronic headaches, but without an ICP-related component, perhaps with migraine features instead. It also includes patients with a seizure disorder that does not precisely localize to the brain adjacent to the cyst. Other situations in this category include static developmental delay and static neurologic symptoms potentially related by location to a cyst, such as static hearing loss associated with an ipsilateral, stable cerebellopontine angle cyst. The treatment of patients in this group is by no means unreported; however, further study and/or observation has also been advocated.¹⁵⁷ Lastly, a group of children will present with large or even very large cysts after an incidental diagnosis and be found to be asymptomatic. Treatment in this group is also controversial, with proposed benefits of reduction in hemorrhage risk and improvement in unrecognized neurocognitive deficits to be balanced against the not insignificant risk for complications.

With specific reference to Galassi type 2 arachnoid cysts, Tamburrini et al surveyed 60 senior pediatric neurosurgeons from Europe, North and South America, and the Near and Far East, presenting a varying clinical scenario to elicit opinions on management. The proposed patient was a 2.7-year-old boy with a left middle fossa type 2 arachnoid cyst. When an asymptomatic, incidental diagnosis was presented, 82% of the participants indicated that they would not recommend surgical intervention; most felt that a follow-up clinic visit and/or MR imaging was indicated. Of the remaining 17%, 13.3% recommended operative intervention to reduce the perceived long-term risk for intracranial hemorrhage. Of the group, 26.5% recommended the avoidance of contact sports in this setting. When the scenario was changed to a potentially symptomatic diagnosis of chronic headaches, about one-third of the respondents recommended surgery without further evaluation, 24% recommended further clinical and/or radiographic follow-up, and the remainder recommended additional study, such as ICP monitoring or dynamic MR imaging. It should be noted that the example patient (2.7 years old) is younger than most patients diagnosed

with a chronic headache syndrome, possibly influencing the survey results. When seizures were considered as the primary presenting complaint, fully a quarter of the respondents recommended surgery, although most did so because of a perceived benefit to avoiding intracranial hemorrhage in a patient prone to head trauma because of the seizures. When a lateralizing EEG was provided, 50% of the respondents said that they would recommend a surgical procedure.¹⁵⁸ It should be noted that opinion surveys like this one are not strong evidence upon which to formulate practice guidelines, but the study does give a good idea of the state of treatment opinion at the time of publication. There are no randomized trials comparing treatment with nontreatment for arachnoid cysts for any of the above indications as of early 2013.

As noted in a previous section, the incidence of intracranial hemorrhage in patients with arachnoid cysts has been reported to be from 0.3 to 6%.^{102,128} Also as noted above, recommendations for prophylactic surgical treatment to avoid the risk for hemorrhage are not uncommon. However, a number of case series report an ongoing risk for intracranial hemorrhage, even after treatment. Spacca et al reported 4 symptomatic late subdural hemorrhages after trauma in a series of 40 patients undergoing endoscopic treatment for middle fossa arachnoid cysts.¹³⁵ In a microsurgical series, Levy et al reported 2 children who required surgical intervention for delayed subdural hemorrhage among 50 treated.¹³⁶ In these series, the rates of hemorrhage from trauma despite treatment (4 to 10%) do not appear to be greatly different from the natural history of the disease. Other series do not report cases of postoperative intracranial hemorrhage after trauma.^{132,159}

Assuming that surgical treatment is indicated, the options include open surgical fenestration,^{159–162} cyst–peritoneal shunt placement,^{79,133,134,138,162} and most recently endoscopic cyst fenestration.^{135,137,162–166}

Surgical Fenestration with Open Microsurgery

The advantages of open surgical fenestration are excellent surgical visualization, a potentially lower risk for intraoperative complications in comparison with endoscopic techniques, and

the use of native CSF pathways rather than permanent shunt hardware. For smaller cysts in eloquent locations, such as the cerebellopontine angle, open surgical fenestration may be the ideal choice. Levy et al described a microsurgical approach to middle fossa arachnoid cysts in which a small temporal craniotomy and extensive sharp microdissection of the basal cisterns were used to expose the internal carotid artery and optic nerve, with fenestration of the arachnoid between the two. The posterior communicating artery and cranial nerve III were exposed, and the membrane of Lilliequist was opened to expose the basilar artery. The authors advised against extensively stripping membranes from the temporal lobe surface.¹³⁶ Helland and Wester reported on 48 patients, 83% treated surgically for presenting complaints of headaches (31%), impaired cognition (27%), and/or seizures (21%). At follow-up, 82% had improved symptomatically while 14% had no improvement and 2 of the 48 worsened clinically despite improved images. On postoperative imaging, 79% of the cysts had resolved or were less than 50% of their baseline size. Self-reported function improved in 67% of patients. Complications were reported as follows: subdural fluid collections in 2 patients, hydrocephalus in 1 patient. The degree of cyst size reduction appeared to correlate with the degree of clinical improvement. The issue of volume reduction versus symptomatic improvement was also addressed by these authors in a series of adult patients, in whom volume reduction did not clearly correlate with outcome.^{118,132} Other comparative series, including the European Cooperative Study, have supported a correlation between cyst size reduction and clinical outcome.¹⁶⁷⁻¹⁶⁹

Levy et al reported on 50 children treated with microsurgical fenestration with a mean follow-up of 3 years. About half of those presenting with epilepsy improved, compared with 67% of those with headaches. A few patients presented with behavioral abnormalities and did not improve. Hypothalamic disturbances improved in about half of the cases. Focal neurologic symptoms, such as sixth nerve palsy and hemiparesis, improved reliably. After surgery, 82% of the cysts decreased in size with treatment, but none completely resolved. Ten percent of patients developed a pseudomeningocele, but this could be managed conservatively. A 6% CSF leak rate was reported. In follow-up, 8% were treated with a CSF shunt for persistent symptoms.¹³⁶

These optimistic reports for open surgery can be contrasted with those of Ciricillo et al, from the University of California, San Francisco, who reported a series of 40 children. Fifteen were treated with fenestration, and two-thirds of these showed no clinical or radiographic improvement and were converted to CSF shunt placement. Of 20 patients initially treated with CSF shunt, 6 required 9 shunt revisions over a median 8-year follow-up.¹³⁴ The authors reported complications of the fenestration procedure that included aseptic meningitis, seizures, cranial nerve III palsy, and subdural hematoma. Complications occurring in patients undergoing shunt placement included protracted nausea and vomiting (6 of 20 patients), aseptic meningitis, and transient cranial nerve VI palsy, believed to be related to ICP changes.¹³⁴

Fewel et al, from the University of California, Los Angeles, reported on 102 patients treated over 20 years. Seventy-three percent of the children treated with open fenestration who did not have associated hydrocephalus at presentation required no

further treatment over the follow-up interval. However, only about one-third of the patients presenting with concomitant arachnoid cysts and hydrocephalus were successfully treated with initial fenestration. The authors recommended combined ventriculoperitoneal shunt placement and cyst fenestration when hydrocephalus was present.¹⁵⁹ Holst et al reported a series of 69 patients treated from 1997 to 2007, comparing all three treatments in a mixed series. Relapse rates after microsurgery were lower (28%) than with shunt treatment (36%) or endoscopy (73%).¹⁶²

Cyst-Peritoneal Shunt

CSF shunt placement has the advantage of being surgically straightforward, with limited blood loss. However, it has the potential disadvantage of exposing the patient to the long-term risk of shunt dependence, although as noted below, a number of authors have reported delayed removal of the cyst shunt after cyst decompression. Although all the techniques report a significant degree of cyst decompression, it is likely that CSF shunt treatment, because of the ability to induce low ICP, offers the opportunity of maximum cyst decompression in comparison with the other techniques. (► Fig. 13.4) Whether this is valuable for outcomes is debated. Arai et al reported on 77 patients who included both adults and children but whose mean age was 12 years. Trepine-size craniotomies were performed, and reachable portions of the outer membrane of the arachnoid cyst were removed. Low-pressure shunts were used without an antisiphon system. Over a mean of 7.7 years, there was marked expansion of the brain, with near-oblivation of even Galassi type 3 cysts. Although symptoms of intracranial hypertension such as headaches and papilledema improved, preoperative cognitive delays did not reliably improve despite resolution of the cysts by imaging. Complications occurred in 11 patients, with 8 patients requiring 13 shunt revisions over a mean 7-year follow-up. An important observation was that at least half of the 8 patients presented with acute symptoms and signs of intracranial hypertension at the time of shunt failure, even though the cyst size was not noted to increase significantly.¹³³ The author has observed a similar phenomenon in his practice. Alexiou et al reported on 89 children undergoing CSF shunt



Fig. 13.4 Anterior fossa arachnoid cysts showing significant resolution after cerebrospinal fluid shunt placement.

treatment for intracranial arachnoid cysts. With 4 patients lost to follow-up, all remaining patients had resolution of their presenting symptoms. Cyst size was reduced in all patients, and to a greater degree in those less than 2 years of age at shunt placement. Thirty-four patients (39%) required shunt revision, 13 of them more than once. Shunt infections occurred in 8.7%. Two patients had a subdural hematoma, and one patient had an intracranial/intracystic hemorrhage after trauma despite shunt placement.¹³⁸

Shim and colleagues reported their experience treating 181 pediatric patients with all three techniques. For middle fossa cysts, shunt placement had the highest rate of obliteration of the cyst but led to shunt dependence, in some cases with shunt failure and increased ICP, without significant change in ventricular size; open and endoscopic techniques were not associated with these complications. However, shunt removal was possible in 8 of 11 patients.¹⁶⁶

Complications of shunt placement in patients with arachnoid cysts appear to mirror those in the general population of patients with hydrocephalus.

Endoscopic Cyst Fenestration

Endoscopic fenestration offers the advantages of shunt avoidance and causes less external tissue disruption in comparison with open surgical techniques. Disadvantages include difficulties with visualizing and controlling hemorrhage and potentially a more limited fenestration, although it has been noted that with the use of angled endoscope lenses, the endoscopic visualization can in some cases exceed what can be achieved with the microscope.¹³⁷ Spacca et al reported on 40 children treated endoscopically from 2001 to 2007. The surgical technique involved stereotactic localization of the operative corridor and fenestration of the optic–carotid and oculomotor triangles. Resolution or improvement of the presenting symptoms occurred in patients with headaches (92%), macrocrania (100%), and focal neurologic deficits (75%). However, developmental delay did not improve in any of the 6 patients who presented with this problem. At a mean follow-up of 27 months, 60% showed a reduction in cyst size. Complications included subdural hygroma in 5 of 30 patients and meningitis in 1 patient.¹³⁵ The use of stereotactic navigation is supported by some^{164,170} but not all authors.¹⁷¹ Turhan et al compared microsurgery with endoscopic treatments for middle fossa arachnoid cysts in a single institution. The groups were unbalanced with respect to cyst size, with more grade 3 lesions treated endoscopically. Imaging follow-up at 1 year disclosed a reduction in cyst size by at least one Galassi grade in all but 2 patients. Complications, most commonly subdural hygroma, were more frequent in the endoscopic group (47%) than in the microsurgical patients (23%).¹³⁷ Mottolese et al reported on 35 children treated with simultaneous shunt placement with an adjustable valve and endoscopic cyst fenestration. In 60%, the cysts disappeared entirely, and in half the shunt could later be removed.¹⁷²

Shunting of arachnoid cysts to the ventricular system^{173,174} and subdural space¹⁷⁵ is also reported. This technique has the theoretical advantage of a more physiologic drainage than shunt placement to an extracerebral cavity, but experience is limited.

Treatment of Suprasellar Arachnoid Cysts

Because of their location, suprasellar cysts more frequently produce hydrocephalus and are more likely to require treatment. Open microsurgery has been reported via subfrontal, pterional, transventricular, and transcallosal routes.¹⁷⁶ Hoffman et al advocated a transcallosal approach because it allowed the cyst to communicate with both the ventricular system and the subarachnoid space, whereas with subfrontal and pterional routes, ventricular entry was difficult.¹⁷⁷ However, the presence of hydrocephalus provides an avenue for endoscopic techniques, which are considerably less invasive. Shunt treatment of the hydrocephalus in this situation without addressing the arachnoid cyst can, unsurprisingly, lead to cyst expansion.¹⁷⁸ As viewed endoscopically, the suprasellar arachnoid cyst wall is often very tough, making direct, unassisted cannulation difficult.¹⁵¹ Stereotactic, radiographic, or endoscopic assistance improves the safety and success of the procedure. Endoscopic procedures allow fenestration of the arachnoid cyst to the ventricular system and fenestration of the cyst to the subarachnoid space from the same approach. Ogiwara et al reported a small series of 6 children treated endoscopically between 2004 and 2011. The main presenting complaint was progressive macrocephaly. In 3 of the 6, cisternal–subarachnoid communication was noted on cisternography. Patients underwent either ventriculocystostomy (VC) or ventriculocystocisternostomy (VCC), with 5 of the 6 experiencing resolution of their presenting complaints and 1 requiring CSF shunt placement.¹⁷⁹ El-Ghandour compared VC with VCC in 25 patients. Treatment with either approach resulted in the resolution of macrocrania and intracranial hypertension in all patients, and in improvements in developmental delay in roughly half. Cyst size reduction was more apparent with VCC than with VC (100% vs. 81%). At a mean follow-up of 4.6 years, recurrence was noted in 27% of the VC patients versus none of the VCC patients.¹⁵¹

Arachnoid cysts of the sella turcica have been successfully managed by a transsphenoidal route with the use of both open and endoscopic techniques.¹⁵³

Treatment of Quadrigeminal and Posterior Fossa Arachnoid Cysts

Quadrigeminal arachnoid cysts are most frequently reported to be approached endoscopically in recently published series.^{180–182} Because these cysts present with a very high incidence of hydrocephalus from posterior third ventricular obstruction, fenestration procedures are often combined with either ETV or CSF shunt placement. A coronal bur hole is used, with the arachnoid cyst seen bulging into the ventricular wall. After fenestration of the cyst to the lateral ventricle, the trajectory allows an ETV to be performed with the same bur hole. Erşahin and Kesikçi treated 17 patients in this fashion. They noted that among patients treated at 6 months of age or younger, a CSF shunt was generally required because of ETV failure, but in only one case did the arachnoid cyst itself require re-treatment. Presenting symptoms of intracranial hypertension and progressive macrocephaly were alleviated in all patients. Infants in this series had severe hydrocephalus at presentation, and 3 developed overdrainage complications that required subdural shunt placement in 2 patients.¹⁸² A second recent report is quite similar.¹⁸¹

Interestingly, despite the location of their cysts, none of the patients in either of these series presented with a defined endocrinopathy. Many patients presenting with endocrinopathy will require exogenous hormone replacement for normal growth and development.¹⁸³

Patients with posterior fossa arachnoid cysts, particularly those in the cerebellopontine angle, are appropriate candidates for open fenestration, given the smaller working space and the proximity of cranial nerves and vascular structures. Shunt placement likely carries with it a higher risk for cranial nerve injury. Jallo et al reported successful open fenestration in 5 children, 3 of whom presented with generalized symptoms of intracranial hypertension and 2 of whom had brainstem and cerebellar symptoms. Following treatment, the generalized symptoms improved, but the cranial neuropathies did not.¹³¹ A pediatric case report of successful endoscopic fenestration of the cerebellopontine angle, with improvement in presenting symptoms of hearing loss and facial weakness, has now appeared.¹⁸⁰

Technique Selection

Among the various surgical techniques, major differences in the likelihood of resolution of the symptoms are not clearly apparent. The choice between them depends, therefore, on complication management, individual surgeon experience, and perhaps long-term goals. For middle fossa cysts in older children, in whom dramatic brain expansion may not be the goal, cyst fenestration by either open or endoscopic technique would appear to be preferable to the long-term risk for shunt dependence. Cyst shunting can be used in cases of fenestration failure. For younger children with much larger cysts, in whom the goal may be brain expansion, this is likely to be more completely accomplished with CSF shunt placement. Whether the hoped-for gains to be achieved by brain expansion in this setting are realistic is still unclear and perhaps not well supported by the available evidence. For patients with suprasellar or quadrigeminal plate arachnoid cysts, an endoscopic approach is likely preferable, although it appears that many infants will need a combination of both endoscopic surgery and cyst shunt placement. Posterior fossa cysts, particularly those in the cerebellopontine angle, are likely better treated in an open fashion.

13.2.7 Outcomes

The natural history and surgical outcomes have been presented individually above. However, to summarize, there is strong evidence that most arachnoid cysts are asymptomatic, rarely expand, and infrequently hemorrhage. In carefully selected symptomatic patients, surgical management appears to be highly successful in resolving symptoms related to intracranial hypertension. It is more difficult to establish that the risk for posttraumatic hemorrhage is reduced, as multiple case reports demonstrate that hemorrhage can still occur after treatment. In addition, although undoubtedly hemorrhage can have severe consequences, most patients reported to have had hemorrhage recover fully, some without surgical treatment.^{102,105,106,128,135,136} It is challenging to be clear about the likelihood that epilepsy will improve after arachnoid cyst treatment in the absence of

the concordant multimodality localization required in other pediatric candidates for epilepsy surgery. The relative consistency with which improvement is reported is encouraging, but in general, the methods of ascertainment and the length of follow-up are not adequate for us to be confident in the results. Treatment to improve preexisting static learning and behavioral difficulties is controversial, with the exception of treatment of the associated hydrocephalus. Several surgical series report improvement,^{132,143,145,146} but others do not.^{133,134} For young patients with very large cysts, it would be valuable to determine if there is a relationship between the degree of decompression and long-term cognitive outcome.

Pearls

- DWM catheters are prone to transcutaneous CSF leaks after initial placement. If a choice is made to place a cyst catheter, care should be taking to minimize the chances of leak by placing shunt hardware away from incisions and by paying attention to shunt valve pressure. Endoscopic options to avoid cyst catheters deserve consideration.
- Headaches and arachnoid cysts are both common and frequently coexist in patients but are not causally related.
- Children with suprasellar arachnoid cysts should undergo endocrinologic evaluation.
- Children less than 4 years of age at the time of diagnosis of an arachnoid cyst are at the highest risk for cyst expansion and should be followed with serial imaging in early childhood. Children older than 4 years at diagnosis are much less likely to exhibit cyst expansion and may reasonably be followed symptomatically.
- The incidence of intracranial hemorrhage in the setting of an arachnoid cyst less than 5 cm in diameter appears to be very low, and most patients who have an intracranial hemorrhage from an arachnoid cyst will recover fully. However, rare patients may present with hemorrhage requiring acute surgical care. Nevertheless, in many cases, an informed patient and family may reasonably accept the low risk for hemorrhage and continue with regular activities, including contact sports.
- Patients with arachnoid cyst shunts may present with significant intracranial hypertension at the time of shunt failure, even with a modest or minimally apparent change in cyst size.

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14 Extracerebral Fluid Collections in Infants

Sandi Lam and David M. Frim

14.1 Introduction and Nomenclature

Many terms, such as benign subdural fluid collections of infancy, benign subdural hygroma, subdural effusion, benign external hydrocephalus (BEH), abnormally enlarged subarachnoid space, and subarachnomegaly, are in use. Many more terms, such as benign subdural collections of infancy, benign extra-axial fluid of infancy, and benign enlargement of the subarachnoid space, attempt to designate the condition as benign based upon radiologic studies alone. The terms benign external hydrocephalus, idiopathic external hydrocephalus, extraventricular obstructive hydrocephalus, and pseudohydrocephalus megaloccephaly include the word hydrocephalus despite minimal or no ventricular enlargement and minimal or no rise in intracranial pressure (ICP). The evolution of progressively better imaging modalities for the extracerebral spaces likely spurred on the process to refine and rename the visualized anatomical spaces and fluid collections over time, resulting in the multitude of terms used for the same or similar conditions. The nomenclature also likely reflects different theories of etiology and outcomes.¹ The terms are summarized in the box “Current and Historical Terms Used to Describe Enlargement of the Subarachnoid Spaces (p. 162).”

Current and Historical Terms Used to Describe Enlargement of the Subarachnoid Spaces

- Benign external hydrocephalus
- External hydrocephalus
- Benign extra-axial fluid collections of infancy
- Idiopathic external hydrocephalus
- Extracerebral fluid collections of infancy
- Pericerebral cerebrospinal fluid collections
- Primitive megalencephaly
- Benign obstructive hydrocephalus
- Subarachnomegaly
- Subdural effusion
- Subdural hematoma
- Subdural hygroma
- Subdural fluid collections of infancy
- Subdural fluid collections
- Pseudohydrocephalus megaloccephaly
- Extracerebral intracranial fluid collections of childhood
- Benign enlargement of subarachnoid spaces

Extracerebral fluid collections in infants reside in the spaces between the pia of the brain and the arachnoid (the subarachnoid space) and in the potential space between the arachnoid and the dura (the subdural space). Imaging of these collections in the infant is usually obtained for the evaluation of a large or enlarging head, as well as many other presentations. Idiopathic enlargement of the subarachnoid space is

commonly considered benign with no clinical or radiographic features suggestive of high ICP. The term *benign external hydrocephalus* (BEH) is the one most commonly used in the published literature. It is used in this chapter to refer to the constellation of findings presented above, although many other names have been applied to this entity. It is important to note that the word *hydrocephalus* is somewhat of a misnomer because BEH is not generally considered a pathologic or surgical diagnosis and is usually self-limited.

14.2 Anatomy of the Extracerebral Space

The anatomy of the extracerebral space can be conceptualized in layers. The pial surface of the brain marks the inner limit of the extracerebral space. The next layer is the arachnoid. Between the pia and the arachnoid is the subarachnoid space, which interdigitates into the cerebral sulci and overlies the cerebral gyri. The subdural space is the potential space outside the arachnoid and underneath the dural lining of the calvarial space.

The subarachnoid space is incompletely divided by arachnoid trabeculae.² The arachnoid and the arachnoid trabeculae are draped over pial vascular anatomical structures to maintain a relatively intact space overlying the entire supratentorial and infratentorial pial surfaces. The arachnoid and arachnoid trabeculae then expand into the extra-axial spaces to create cisterns.

The surface cerebrovascular tree of both large and medium-size arteries and veins is contained within the subarachnoid space. The arterial half of the subarachnoid vasculature enters the subarachnoid space essentially upon entering the cranial vault and subdural space. The arterial vasculature comes from both the carotid circulation and the vertebral circulation. The arterial tree is spread over the pial surface and penetrates the brain parenchyma at intervals to supply blood to the intraparenchymal capillary circulation of the brain.

Cerebral venous flow then goes in the other direction from the intraparenchymal capillary bed out of the brain parenchyma into the folds of the sulci and then into the subarachnoid space. Here, the veins coalesce and insert into large intradural venous sinuses. The venous subarachnoid vascular tree pierces through the arachnoid surface in many places into the true subdural space to feed directly into dural veins and venous lakes. These can be found as the veins enlarge and move closer to the large venous sinus structures, such as the superior sagittal sinus and the petrosal sinuses along the temporal bone.³ The Virchow-Robin spaces of cerebrospinal fluid (CSF), which are around the small blood vessels in the intraparenchymal space, may in fact be an extension of the subarachnoid CSF spaces along the brain-penetrating portions of the arteries.⁴ The relationship of these spaces to the enlargement of the subarachnoid space is not well understood.

The subdural space is a potential space in which the only recognized structure between the arachnoid and the dura is a segment of dural bridging veins. There may be a small amount

of CSF from an incompetent arachnoid membrane or from tracking along the traversing veins. The total length of the extra-arachnoid segment tends to increase as these veins approach the large venous sinuses. Any significant collection of fluid or other material, such as blood, in the subdural space is pathologic. There is no universally accepted or generally known function for the subdural space or the material within it.

14.3 Imaging of the Subdural Extra-arachnoid Space

14.3.1 Radiographic Anatomy and Imaging Characteristics of Benign Extracerebral Fluid Collections

Magnetic resonance (MR) imaging is the gold standard imaging modality for identifying the subarachnoid space versus the subdural extra-arachnoid space.⁵⁻⁸ Particularly on T2-weighted sections, traversing cortical veins can be visualized within subarachnoid fluid collections at the cerebral convexities; this is referred to as the “cortical vein” sign^{5,9} (► Fig. 14.1).

The arachnoid membrane overlying the subarachnoid space cannot be seen on the MR image unless pathologic fluid or other material exists on top of it in the subdural space, as in chronic subdural hematoma (► Fig. 14.2). Fluid in the subarachnoid space can clearly be differentiated from fluid or other material in the subdural space by the presence of a visible arachnoid membrane. Fluid in these spaces can be differentiated from CSF based on MR imaging signal intensity.⁸ The ability of MR imaging to discern various densities of protein within the fluid allows a much more detailed determination of the exact anatomical location of CSF versus other types of fluid.⁵

The subarachnoid space takes the shape of the gyri of the underlying brain, whereas the inferior boundary of the subdural space is smooth. Because of arachnoid trabeculae at the cortical sulci, the subdural space cannot interdigitate into the sulci. In cases of chronic subdural hematoma, the cortical vein sign is not present. Computed tomography (CT) as a

modality for identifying extracerebral fluids is less sensitive than MR imaging because the vessels of the subarachnoid space are more difficult to visualize. CT can identify 90% of subdural fluid collections, whereas MR imaging is estimated to be 100% sensitive.¹⁰

In infants with open fontanels, the distance between the dura and the pial surface of the brain can easily be assessed by transfontanel ultrasonography.^{11,12} However, the examination is limited to the cone of ultrasonographic vision through the fontanel, as well as being limited by artifact from the skull bone.

Clinically, it is difficult to draw conclusions about the exact anatomical location of the fluid in the extracerebral space or the nature of that fluid without MR imaging or, when needed, analysis of a fluid sample drawn percutaneously. Intravenous contrast neuroimaging studies show the rapid influx of contrast medium from CSF into the subarachnoid fluid spaces but not into fluid in the subdural extra-arachnoid compartment.¹³

The frontal subarachnoid spaces are enlarged beyond the upper defined limits for age in the setting of benign extracerebral fluid collections, and the cortical vein sign is visible on T2-weighted MR imaging. The ventricles are generally normal or moderately enlarged in size. The interhemispheric fissure is often but not always wider than normal; as well, the third ventricle and basal cisterns are larger than normal.¹⁴⁻¹⁷

Benign extracerebral fluid collections can be distinguished from global cerebral atrophy because the latter is associated with widening of the cerebral sulci globally and, not concentrated in the nondependent subarachnoid space, such as the frontal areas visualized in a supine patient.¹⁵ As well, cerebral atrophy is not associated with increasing head circumference.

14.3.2 Normal Measurements of the Subarachnoid Space

There is no consensus on the definition of normal subarachnoid space size. There is no significant difference between reported subarachnoid space sizes in male and female children.¹⁸⁻²⁰ In neonates, the maximal upper measurement limit of the

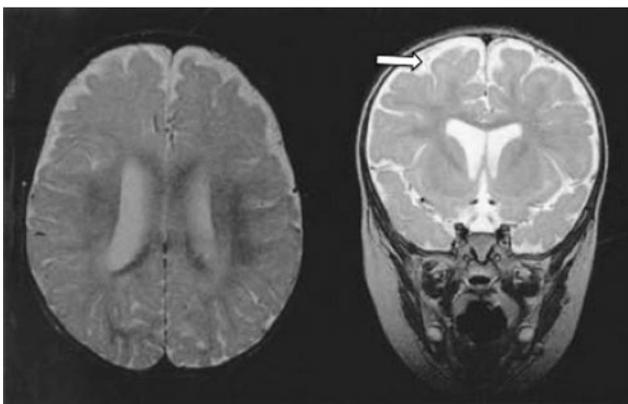


Fig. 14.1 Enlarged subarachnoid spaces. Axial and coronal T2-weighted high-resolution magnetic resonance images of the brain demonstrating enlargement of the subarachnoid space. Note the visible arachnoid layer, with most of the vessels (*arrow*) beneath it and only the dura above it.

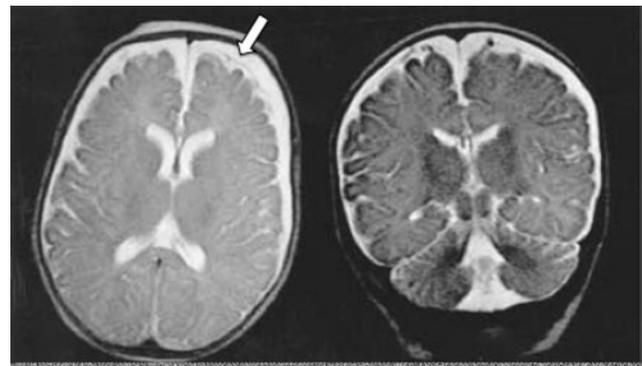


Fig. 14.2 Chronic subdural hematoma. Axial and coronal T2-weighted high-resolution magnetic resonance images of the brain demonstrating bilateral chronic subdural hematomas in the late phase. Note the visible arachnoid layer (*arrow*) displaced downward by a fluid layer between it and the dura. Cortical vessels are not visualized within the fluid of this chronic subdural hematoma. Any significant amount of fluid in this space is pathologic.

subarachnoid space width is reported to range from 3.3 to 5 mm.^{18,20,21} In infants younger than 1 year old, the maximal upper limit of normal subarachnoid space width is reported to range from 4 to 10 mm.^{16,19,22–24} Upper values for the interhemispheric fissure width range from 6 to 8.5 mm, and for the distance between the lateral wall of the superior sagittal sinus and the cortical surface (sinocortical width), they range from 2 to 10 mm.^{1,22–26} Variations in the size of the subarachnoid spaces are observed during growth, with the upper limit of normal width reported to increase from birth to 7 months,¹⁹ to decrease from 1 to 2 years of age,²³ and to become essentially absent after 2 years of age.^{27–29}

14.4 Identification and Pathophysiology of Fluid within the Extracerebral Spaces of the Infant

14.4.1 Identification

Fluid within the subarachnoid space in the nonpathologic state is CSF. Other fluids that can be present within the subarachnoid space endogenously are blood products or pus from a purulent infection of the surface of the brain. Fluid within the subdural space that is purely extra-arachnoid can be CSF transudate, blood (such as from rupture of a subdural bridging vein), blood transudate, or purulent material from an extra-arachnoid subdural abscess. Blood in its acute state in the subarachnoid or subdural space can be solid or gelatinous clot. The treatment of acute subdural hematoma or acute subarachnoid hemorrhage is outside the scope of this chapter and is discussed elsewhere in this volume. Once subdural or subarachnoid blood lyses to become a proteinaceous liquid, it falls within the rubric of an extracerebral fluid collection. Nongelatinous hemorrhage within the subarachnoid space tends to resolve over days to weeks because the subarachnoid space is a low-flow CSF space,^{30,31} whereas hemorrhage in the subdural space can take much longer to resolve because of the absence of CSF flow. Rupture of the arachnoid membrane, from trauma or surgical manipulation, fuses the subdural and the subarachnoid space for a time before the brain itself has the opportunity to scar to the underside of the dura, which may frequently happen. In that situation, in which the anatomical boundaries are blurred, the fluid mixture is more difficult to diagnose but can be some combination of CSF, blood, and pus.

Blood in the subdural space undergoes a transition from solid clot to eventual resolution by lysis and resorption. During this progression, the blood can become bounded with subdural membranes, which are a fibrous encapsulation of the original clot that is vascularized.^{32,33} There is extensive literature on subdural membranes and their development and resolution. The membranes tend to enhance with gadolinium.^{34,35} The membranes also elaborate tissue plasminogen activator (tPA) and bradykinin, which can cause further or recurrent hemorrhage, spilling more and more blood into the subdural space.^{36,37} This creates a laminar hierarchy of hemorrhages in various states of resorption, with intervening membranes that become progressively thinner with time. The anatomical localization of these membranes also becomes farther and farther away from

the dura, which appears to be the origin of their blood supply.³⁸ The stages of resolution of subdural hematomas have been well described in the literature.^{39,40}

Infection within the subdural space can be gelatinous, fluid, or a combination of both. The most accurate term for this infection is *subdural empyema*. Subdural empyema can involve both the subdural space and the subarachnoid space, which is observed on imaging and during intraoperative inspection.^{41,42} It is frequently associated with sinusitis and is thought to migrate along the valveless veins in the subdural space.^{42,43} The term *subdural effusion* has been used to describe a hypodense fluid accumulation associated with meningitis, such as in the case of *Haemophilus influenzae* infection.⁴⁴ The term *subdural effusion* has also been applied to hypodense subdural fluid collections in the setting of trauma, adding ambiguity to the terminology used for these lesions. No matter what scheme of nomenclature is used, the anatomical components of the extracerebral space are as presented, and the fluid can comprise only CSF, blood (either acute or during a phase of resolution), or an exudate from a blood clot or an abscess. This concept allows a simplified interpretation of the nomenclature and of the pathologic entities involved.

14.4.2 Pathophysiology

A number of theories about the pathophysiology of BEH exist, although the etiology is not completely understood. The most common theory is that the arachnoid villi are not mature, with a resultant inability to absorb CSF effectively, which leads to CSF accumulation in the subarachnoid space.⁴⁵ With a relative impediment to the low-pressure resorption of CSF from the subarachnoid space through the arachnoid into the superior sagittal sinus, the subarachnoid space enlarges. The ventricles of the infant with an enlarged subarachnoid space may also appear to be mildly dilated and at the upper limit of normal.^{46,47} The sylvian fissures and sulci are also slightly enlarged. As the cranial sutures are not fused in this age group and the skull is compliant, a marked increase in ICP is generally avoided, whereas macrocephaly is common. Heredity is suggested to play a role, as more than 40% of children with BEH are reported to have a familial form, with one or more close relatives being macrocephalic and having a head circumference at or near the 98th percentile.^{5,28,46,48–52} BEH also reported to occur in twins and triplets. The phenotype may be related to delayed maturation of the arachnoid villi.¹⁵ Follow-up evaluation of many of these patients shows that the parenchymal brain volume appears to conform to a normal configuration by 3 or 4 years of age,^{28,29} supporting spontaneous resolution of an underlying problem, such as immature arachnoid villi, which mature at age 18 months.^{1,53}

Supporting the idea of mildly impaired CSF resorption is the observation that conditions with increased central venous pressure, such as right-sided heart failure and pulmonary disease, enlarge the subarachnoid spaces, presumably through impeded resorption.^{15,54,55} (► Fig. 14.3) Additional correlation between increased CSF spaces and rigid venous outflow impedance comes from observations in craniosynostoses, plagiocephaly, and hydrocephalic achondroplastic dwarfs.^{56–59}

Enlarged subarachnoid spaces may be on the spectrum preceding internal hydrocephalus in children with communicating

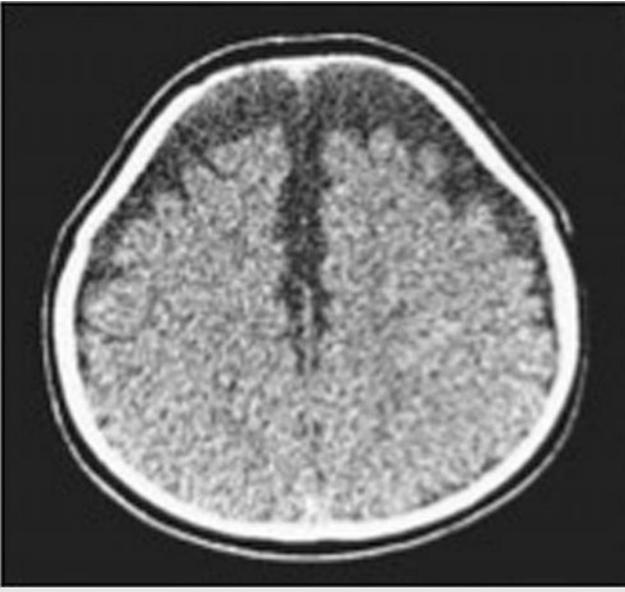


Fig. 14.3 Axial noninfused computed tomographic scan of the head of a 3-month-old girl with right-sided heart failure and a bulging fontanel demonstrating enlargement of the subarachnoid space.

hydrocephalus if the arachnoid granulations remain dysfunctional, with CSF accumulating in the subarachnoid space and then subsequently in the ventricular system over time.^{29,60} However, there is a distinction between delayed maturation of the arachnoid villi with regression of the problem after the age of 18 months and agenesis of the arachnoid villi with necessity for surgical CSF diversion.^{53,61}

Another theory for the pathophysiology of BEH is cranioccephalic disproportion, with the skull transiently growing at a faster rate than the brain. The brain growth is believed to be slow in these children, and after a lag period, the brain begins again to fill the cranium.^{15,50,62,63}

The developmental pathophysiology of benign enlargement of the subarachnoid spaces is not completely understood. In our experience, BEH has not progressed to frank hydrocephalus with an enlarged fluid space under inappropriately high pressure unless it is complicated by infection or hemorrhage; however, such rare occurrences have been reported in the literature.^{46,64–66} In the setting of presumed mild malabsorption of fluid, a small amount of blood mixed into the subarachnoid CSF can cause the pressure to increase, so that extracranial shunting is eventually required, as in absorptive hydrocephalus with ventricular enlargement having other causes.²⁹ Purely subdural bleeding might not lead to such a problem because it would not mix with the CSF in the subarachnoid space.

Blood found in the subdural space is generally thought to come from the disruption of bridging veins, which penetrate the arachnoid after draining the cortical surface and then insert into the underside of the dura or directly into a dural venous sinus structure.⁶⁷ Various issues around the acute management of subdural hematoma are discussed in other chapters. As an extracerebral fluid collection, subdural blood can be of small volume or can mix with the CSF of a ruptured arachnoid membrane. As a purely subdural collection, blood will coagulate and then organize into a mature clot. At that

point, it may become encapsulated by membranes and then be slowly reabsorbed. A chronic subdural hematoma is not stable because ongoing bleeding from the membranes can increase the size of the fluid collection and turn a relatively small initial hemorrhage into a lesion causing mass effect.⁶⁸ It can also increase the tension on already stretched veins, leading to repeated rupture from minor trauma or inertial changes. As the blood is resorbed, the fluid collection will become less dense, a change visible on CT and MR imaging; however, it can easily be differentiated from BEH by the lack of visible subarachnoid vessels (i.e., no cortical vein sign). The vessels in the subarachnoid space would not enter into an isodense chronic subdural hematoma in its late phase.

A connection between BEH in childhood and the development of normal-pressure hydrocephalus (NPH) in the elderly has been suggested, with a two-hit hypothesis of childhood BEH followed by deep white matter ischemia leading to symptoms in later years.⁶⁹ Patients with NPH have significantly larger intracranial volumes than control subjects on imaging,⁷⁰ and 20% of patients with NPH have head circumference measurements over the 90th percentile.⁷¹ The possible link between BEH and later NPH has yet to be fully explored and may offer future insights into natural history and management.

14.4.3 Associated Conditions

BEH has been associated with developmental delay^{50,72–76} and an increased theoretical and observed risk for subdural hematoma.^{7,77–79} Other reported associations include prematurity and intraventricular hemorrhage,^{80–83} meningitis,^{81,84} metabolic disorders,^{85,86} and certain medications, such as chemotherapeutic agents.⁸⁷ BEH has also been associated with raised venous pressure, such as in systemic disease, thoracic conditions, and right-sided heart failure.^{15,54,55} Rigid venous outflow obstruction and thus raised venous pressure in craniosynostoses, plagiocephaly, and achondroplasia have been reported to cause external hydrocephalus.^{56–59} Syndromes associated with enlarged subarachnoid spaces include achondroplasia, Sotos syndrome, Beckwith syndrome, Weaver syndrome, and Goldenhar syndrome.²⁸

Fetal MR imaging studies show that 19% of those with mild ventriculomegaly and large subarachnoid spaces prenatally later carried a diagnosis of BEH as infants.⁴⁷ The prominent subarachnoid spaces seen prenatally are distributed more posteriorly; this pattern reflects the formation of the subarachnoid space as a cavitation of the primitive meninges from the ventral to the dorsal portion of the neural tube.⁸⁸

14.4.4 Implications for the Evaluation and Diagnosis of Nonaccidental Head Trauma

Although isolated subdural hematoma without a known intervening trauma can be a sign of nonaccidental trauma, it appears that our knowledge of the pathophysiologic mechanisms for subdural hematoma in the setting of preexisting BEH is incomplete. There are ongoing investigations on the infant shaking impact syndrome.^{89–91} BEH may predispose toward subdural hematoma from an impact that would otherwise not cause a

subdural hematoma in a child with normal-size subarachnoid spaces. The proposed etiology is stretching of bridging veins in the enlarged subarachnoid spaces. The risk for developing subdural hematoma is reported to be higher in children with BEH after minimal or no trauma to the head.^{6,7,78,79} Because of these observations, subdural hematoma is not considered pathognomonic for nonaccidental trauma in situations in which BEH is present. A careful search for other evidence in the context of a full evaluation for nonaccidental trauma must be made in the patient with BEH and subdural hematoma before child abuse is diagnosed. In the absence of other evidence, the diagnosis of nonaccidental trauma cannot be based solely on the presence of a chronic subdural fluid collection in a child with BEH and no history of significant head impact.

14.5 Epidemiology

The incidence and prevalence of BEH are not known. A review of the records of a tertiary pediatric neurology practice notes that 0.6% of patients were diagnosed with BEH.⁹² Approximately two-thirds of children with BEH are male.^{48,93} BEH is reported to be the most common cause of macrocephaly in infants in developed countries.^{28,94}

Most studies report a familial pattern, and from 40 to 80% of children with BEH have at least one close relative with macrocephaly and a head circumference measuring above the 98th percentile.^{5,28,46,48-52} BEH has been reported in twins and triplets, suggesting a genetic component.^{31,95} The inheritance pattern is postulated to be autosomal-dominant or multifactorial, with a gene exerting an effect during a limited period of susceptibility in development, such as a delay in the maturation of arachnoid villi.^{15,60,96}

14.6 Clinical Presentation of Extracerebral Fluid Collections in the Infant

Extracerebral fluid collections can present like any intracranial mass lesion. In BEH, the presentation is recognized by a large head circumference that may be crossing percentile markings in the first several months of life.^{28,62,76} The fontanel will generally be soft and will be concave upon sitting. The sutures will not be split. Occasionally, the child may also present with positional plagiocephaly, which has a correlation with BEH⁵⁸ (► Fig. 14.4).

Most commonly, the growth trend in the head circumference of a child with BEH stabilizes in relation to the percentile growth curves by 18 months of age. Children with BEH who have had radiographic follow-up demonstrated spontaneous resolution of frontal subarachnoid enlargement within 2 to 3 years, with no recurrence of the enlarged subarachnoid fluid space once it resolved.^{14,15,29,49,97}

The child with BEH may have gross motor delay consistent with a large head, which may decrease the child's ability to move and roll early in life. This delay should disappear as the proportion between the head and the body changes with growth. In addition to delay in gross motor skills, delay in

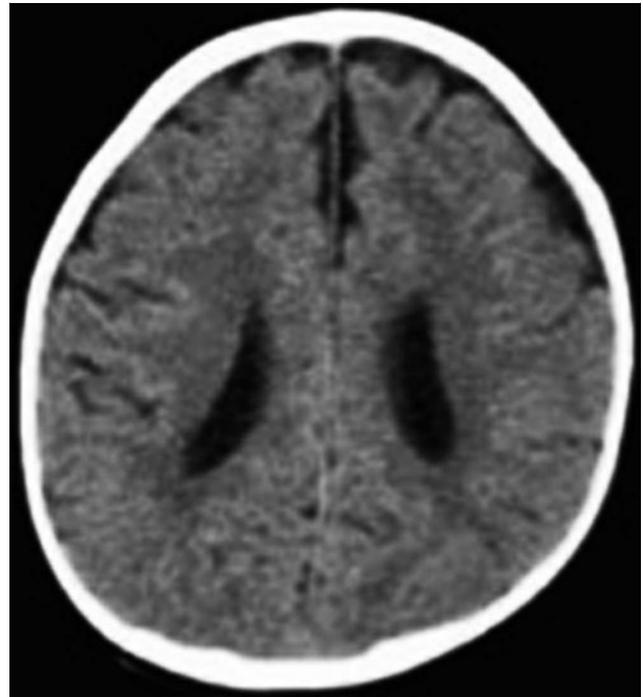


Fig. 14.4 Axial nonfused computed tomographic (CT) scan of the head of a 6-month-old boy with occipital plagiocephaly. CT scan demonstrates enlarged subarachnoid spaces, which are reported to be associated with positional plagiocephaly.

speech and language and other neuropsychological delay have been reported. Most of these delays are reported to decrease or disappear in 1 to 4 years. In a review of the literature, up to 17% of children with 2- to 5-year follow-up had abnormal psychomotor development.^{1,72,97}

Bleeding into the enlarged subarachnoid space, either externally from disruption of the arachnoid membrane after trauma with concurrent subdural hematoma or internally from subarachnoid hemorrhage, may cause progressive hydrocephalus. The clinical presentation at this point would be that of raised ICP in an infant, including convex bulging of the fontanel, splitting of the sutures, and rapid head growth. Other signs of increased ICP, such as irritability, may also be present.

Blood in the subdural space can cause cortical irritation leading to seizure.⁹⁸ Subdural hematomas can also enlarge to cause mass effect and focal neurologic deficits, such as hemiparesis. In its more indolent form, an enlarging chronic subdural hematoma can cause convex bulging of the fontanel and splitting of the sutures, as does any enlarging fluid collection in the brain of an infant. The presence of a subdural hematoma in a child with increased subarachnoid space may not follow recognized head trauma.^{7,77,79} The predisposition of children with BEH to subdural hematoma has been recognized. A potential etiologic factor may be the increased length of the subarachnoid and subdural veins. This allows prediction based on mathematical modeling of venous disruption, with relatively less impact to the cranium than would happen in children with thinner subarachnoid spaces and shorter veins.⁷⁷ Implications for the investigation of nonaccidental head trauma are aforementioned.

14.7 Treatment of Extracerebral Fluid Collections in the Infant

It is important to note that no randomized controlled studies exist comparing treatment and nontreatment for BEH. A large majority of children are managed conservatively. No comparative studies or large-scale cohort studies have been done to examine the effect of observation or of intervention on BEH. Neuropsychological testing, developmental assessments, and long-term follow-up in larger studies are needed to further understand this entity.

BEH usually has a benign course and is self-limited. Only when it progresses to a true malabsorptive hydrocephalus does it require any sort of fluid diversion. In the absence of some additional factor that decreases the amount of CSF absorbed from an enlarged subarachnoid space, typically no treatment is indicated for enlarged subarachnoid spaces. In the situation of traumatic hemorrhage mixing into the CSF of a patient with enlarged subarachnoid spaces, there may be a transient period of elevated ICP that can be treated by one or more percutaneous taps into the extracerebral space.⁶⁸ If a chronic subdural collection develops, it may also require several days of continuous external drainage to obliterate the extracerebral space and make the recurrence of elevated ICP from subdural fluid unlikely.⁹⁹ It is rare, but the persistence of extra-axial fluid collections can require temporary, self-contained shunt placement.^{100,101}

Bleeding into the subdural space from the rupture of a subdural bridging vein can be an acute problem presenting with life-threatening intracranial hypertension. The treatment of this problem is discussed elsewhere in this volume.

A loculate fluid collection in the extra-axial space on imaging after a distant trauma or unrecognized trauma is likely to be a chronic subdural hematoma. The diagnosis can be made based on percutaneous subdural tapping, which will yield bloody fluid with xanthochromia. If the chronic subdural hematoma is in its late phase, such a tap may reveal only a clear yellow fluid. Concurrent lumbar puncture may show clear CSF, or if the arachnoid membrane was ruptured by the initial trauma, the CSF throughout the neural axis may be of the same color. Because the subdural space is anatomically separate from the subarachnoid space, we emphasize that blood wholly in the subdural space should not cause hydrocephalus; although in its late phase, the chronic subdural hematoma can enlarge and cause mass effect as a loculate fluid collection. This will need treatment by continuous drainage for several days,⁹⁹ which will obliterate the space (especially when it is membrane-bound). The historical approach of “stripping the subdural membranes” in this situation may not be necessary, as entry into all loculate spaces with bur hole or percutaneous drainage may suffice to obliterate loculation. Continuous drainage through a subdural drain to an external collection bag may allow obliteration of the space and approximation of the layers of the subdural collection, where they will scar together. Needle aspiration has been used in the past but has been reported to be rarely effective as definitive management; therefore, it is reserved for use as a diagnostic measure.¹⁰²⁻¹⁰⁴ We recommend the treatment of symptomatic bilateral chronic subdural

hematomas with continuous external drainage for up to 7 days with standard ventricular catheters and careful attention to electrolyte balance and infection avoidance. If fluid drainage ceases before 7 days and CT shows obliteration of the subdural space, the drains may be removed earlier. Occasionally, the treatment of a chronic subdural hematoma in its late phase may necessitate a subdural-to-peritoneal shunting device. If the subdural collections return following drain removal, placement of a unilateral subdural-to-peritoneal shunt with a low-pressure valve is recommended.¹⁰⁵ Follow-up CT is recommended 1 month after shunt placement to ensure bilateral drainage from a unilateral shunt. The need for subdural fluid diversion is often not permanent, which may reflect resolution of the inflammation in the absorptive surface or obliteration of the subdural space. Although not required, the shunting device may eventually be removed to avoid future shunt-related complications.

A common scenario encountered by the practicing neurosurgeon is an infant with macrocephaly and mild developmental delay whose CT scan shows BEH and mild ventriculomegaly. The assessment of such a patient should begin with the history, a physical examination, and a thorough radiologic evaluation. The history and physical examination can distinguish between congenital, traumatic, and infectious etiologies; the family history can assess syndromic causes and familial macrocephaly. In particular, careful measurement and charting of the parental head circumference may reveal familial macrocephaly, which is commonly associated with BEH, with emphasis on the benign course. In many cases, this may allow the cessation of further work-up in favor of a period of observation.

High-resolution coronal T2-weighted MR imaging can distinguish between BEH, chronic subdural hematoma, and an infectious subdural fluid collection. If idiopathic BEH is diagnosed, then a careful evaluation of the degree of developmental delay should be made. If the developmental delay is limited to deficiencies in head control based on an altered center of gravity in an infant with macrocephaly, then conservative observation is recommended. However, if the developmental delay is more profound, then a lumbar puncture may be warranted, although the results of a lumbar puncture may be difficult to interpret with respect to the present literature on the topic.

A review of the literature on external hydrocephalus shows a lack of consensus concerning the role of raised ICP, likely because of the inclusion of heterogeneous groups in the studies of this condition. Few studies report direct measures of intracranial or intrathecal pressure.^{51,75,106} In these reports, an effort was made to exclude hydrocephalus and other syndromic, traumatic, or infectious macrocephalic etiologies. The ICP values reported range from normal to slightly increased, from 6 to 16 mm Hg.¹ Other articles examining macrocephaly and BEH used indirect evidence of raised ICP, such as bulging fontanel, engorged scalp veins, and clinical improvement after medical or surgical treatment. Twenty-five patients showed some signs and symptoms of raised ICP,^{45,73,107} and 39 showed a lack of evidence of intracranial hypertension.^{45,50,82} These data are confounded by the combination of chronic hematomas, effusions, and syndromic macrocephaly. As well, the possibility of raised venous pressure creating BEH must be identified and, if possible, treated.¹⁰⁸

Increased ICP, defined as an opening pressure greater than 15 cm H₂O, appears in the minority of cases of BEH in the literature. This should require treatment, typically with the placement of a CSF shunt. Some studies discuss medical management with acetazolamide (Diamox; Teva, North Wales, PA), but only short-term improvement is reported.^{14,45,109} Good outcomes are reported from shunting, although these cannot be interpreted meaningfully as the cases illustrated are highly selected and represent a small and heterogeneous group. As external hydrocephalus is thought to be due to disturbances of CSF absorption (see section on pathophysiology) and thus anatomically can be classified as a communicating hydrocephalus, insertion of a ventriculoperitoneal shunt is the most appropriate intervention when surgical treatment is indicated.^{1,110} Lumbar-peritoneal shunting is not recommended and has been associated with the potential for ventriculomegaly in this scenario.¹¹¹ Subdural-to-peritoneal shunting is also not recommended for external hydrocephalus as it does not directly address the CSF compartment; the CSF in BEH lies in the subarachnoid space, not the subdural space. We recommend ventriculoperitoneal shunt placement in the instances when infants with enlarged extracerebral subarachnoid spaces exhibit signs and symptoms of increased ICP requiring surgical treatment.

14.8 Conclusion

Significant nomenclature exists to describe extracerebral fluid collections in young children. When the naming of this finding is based on the anatomy of the subarachnoid and subdural spaces, the major entities that comprise extracerebral fluid collections are benign external hydrocephalus, chronic subdural hematoma in early and late phase, and subdural empyema. Once the pathophysiology is clearly delineated, its evaluation, diagnosis, and treatment generally follow logically, although the etiology of benign external hydrocephalus is not completely understood.

Pearls

- Macrocephaly in an infant with enlarged subarachnoid spaces is usually benign. High-resolution T2-weighted MR imaging is most useful in distinguishing macrocephaly from chronic subdural hematoma in the late phase.
- When BEH is encountered, look for familial macrocephaly, right-sided heart disease or pulmonary disease, or prematurity as an associated etiology. Developmental delay needs to be evaluated.
- The parents of children with BEH should be advised about the theoretically increased risk for hemorrhage into the enlarged subarachnoid spaces in minor head trauma and for the association between BEH and positional head molding.
- Chronic subdural hematoma in the late phase can cause elevated intracranial pressure and requires drainage percutaneously, by external drainage, or by subdural-to-peritoneal shunt placement.
- Isolated, unexplained subdural hematoma in a relatively healthy child with underlying BEH cannot be considered pathognomonic for nonaccidental trauma in the absence of other medical or social evidence suggestive of abuse.

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15 Congenital Intracranial Malformations

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Congenital malformations of the brain comprise a large and diverse set of anomalies that result in a wide range of functional outcomes for affected children—ranging from relatively benign neurologic deficits to severe deficits that are incompatible with life. The nervous system develops in an orchestrated manner, regulated by numerous proteins that signal the proliferation, migration, and differentiation of primordial cells into the functioning neurons and supporting structures that make up the human nervous system. Cerebral malformations, thus, can result from dysfunction along this highly regulated embryogenic pathway through genetic, metabolic, infectious, and in utero environmental abnormalities. Advances in neuroimaging make possible the identification of more subtle malformations. In addition, the increasing availability of high-resolution microarray-based comparative genomic hybridization (aCGH) genetic testing has allowed a more precise diagnosis than ever before. In fact, the explosion in our knowledge of the genetic and molecular controls involved in brain development is shedding new light on the etiologies of congenital malformations, raising the possibility of improving our management of these often devastating conditions.

Based on the current understanding of abnormal embryology, the major malformations are grouped as supratentorial or infratentorial (see boxes “Classification of Supratentorial Malformations (p. 171)” and “Classification of Infratentorial Malformations (p. 171)”). As we continue to gain more knowledge of the developing brain in the future, the classification will likely be altered. A detailed description of the development of the central nervous system (CNS) is covered in another chapter. We discuss embryology only briefly here as it pertains to the various congenital malformations. The chapter concludes with some general comments and recommendations regarding their diagnosis and surgical management.

Classification of Supratentorial Malformations

- Disorders of neurulation
 - Anencephaly, craniorachischisis
 - Cephalocele (encephalocele)
 - Congenital dermal sinus
- Disorders of ventral induction
 - Holoprosencephaly
 - Septo-optic dysplasia
 - Dysgenesis of the corpus callosum
- Abnormal neuronal proliferation or apoptosis
 - Reduced proliferation or excess apoptosis
 - Microcephaly
 - Microlissencephaly
 - Megalencephaly
 - Cortical dysgenesis with abnormal cell proliferation
 - Hemimegalencephaly
 - Type 2 focal cortical dysplasia
 - Congenital neoplasia
- Abnormal neuronal migration
 - Neuroependymal abnormality

- Periventricular (subependymal) heterotopia
- Abnormal transmantle migration
 - Lissencephaly/subcortical band heterotopia
- Abnormal late transmantle migration
 - Subcortical heterotopia
- Abnormal terminal migration
 - Cobblestone complex
- Abnormal postmigrational development
 - Polymicrogyria
 - Polymicrogyria with schizencephaly
 - Polymicrogyria without schizencephaly
 - Focal cortical dysplasia
 - Type 1 focal cortical dysplasia
 - Type 2 focal cortical dysplasia
 - Microcephaly

Data from Barkovich et al.^{60,90}

Classification of Infratentorial Malformations

- Malformations of the midbrain and hindbrain
 - Molar tooth sign malformations
 - Joubert syndrome
 - Joubert syndrome–related disorders
 - Rhombencephalosynapsis
- Malformation of the cerebellum
 - Cerebellar dysplasia
 - Lhermitte-Duclos disease
 - Migration disorders
 - Vermis and cerebellar hemisphere hypoplasia
 - Focal
 - Diffuse (e.g., Dandy-Walker malformation)
 - Cerebellar vermis hypoplasia
 - Isolated
 - Syndromic
- Malformation of the pons and cerebellum
 - Pontocerebellar hypoplasia

Data from Parisi and Dobyns.¹³⁶

15.1 Types of Congenital Intracranial Malformations

15.1.1 Anencephaly

Anencephaly is the most severe of the neural tube defects (NTDs), resulting in the absence of major portions of the brain and skull. Like craniorachischisis and spina bifida, anencephaly occurs when the rostral neural tube fails to close. Apposition and fusion of the neural apices at the dorsal midline occur between the third and fourth weeks of gestation. The fusion begins at the primitive hindbrain–cervical junction, referred to as

closure 1, and spreads in both a rostral and a caudal direction. Additional points of fusion occur at the most cephalic end of the embryo, known as closure 3, and at a variable location between closures 1 and 3, known as closure 2.^{1,2} A defect in fusion of the anterior neuropore, between closures 1 and 3, at approximately gestational day 24, results in anencephaly (► Table 15.1).³ Initially, a rudimentary cerebrum can exist, resulting in what is known as anencephaly (► Fig. 15.1), but the exposed brain is subject to injury from amniotic fluid and in utero mechanical trauma. As a result, stillbirths are common with anencephaly, but a third of affected fetuses are born alive. Unfortunately, there is no effective treatment, and these newborns survive only hours. They are thought to be not capable of consciousness or of experiencing pain owing to the lack of cerebral development.⁴

The diagnosis of anencephaly can be made prenatally by screening alpha fetoprotein and ultrasound. Currently, anencephaly occurs an estimated 1 in 1,000 births in the United States,^{5,6} although there are significant geographic, racial, and socioeconomic variations. However, because of the option of pregnancy termination after prenatal diagnosis, the exact incidence is difficult to determine. The introduction of maternal folic acid supplementation has resulted in a significant decline of NTDs worldwide, including anencephaly.

15.1.2 Cephalocele

A cephalocele (or encephalocele) is a rare form of NTD in which the cranial contents protrude through a congenital defect in the cranium. It can be further classified based on the contents. A cranial meningocele contains only meninges, whereas an encephalomeningocele or encephalocele contains both meninges and brain tissue (► Fig. 15.2). An encephalocystocele or hydrencephalomeningocele also includes a dilated ventricle. These malformations are a result of failure of the neuroectoderm to separate from the surface ectoderm during neural tube closure, which leads to a mesodermal defect and prevents proper ossification of the skull. If the skull defect is sizeable, meninges and brain can herniate through the opening, resulting in a meningocele or cephalocele. The sac, which is often at the midline, is covered by normal or dysplastic skin, and thus, maternal serum alpha fetoprotein is typically normal. Cephaloceles in the occiput are most often seen in North America, and those in the frontal region, particularly the nasofrontal, nasoethmoidal, or naso-orbital region, are common in Southeast Asia, certain parts of India, and Africa.^{7,8} The prognosis depends on the location of the lesion, the presence and size of brain herniation, and other congenital anomalies. Cephaloceles can be associated with cerebellar dysplasia, lissencephaly, hypoplastic brainstem,

Table 15.1 Embryology of major brain malformations

Gestational age	Normal development	Malformation	Genes
Development of the hemispheres			
3–4 weeks	Primary neurulation	Anencephaly Cephalocele Congenital dermal sinus	
6 weeks	Prosencephalic cleavage	Holoprosencephaly	<i>SHH, SIX3, TGIF, ZIC2, PTCH, BMP, HPE1, HPE6, HPE8</i>
6–12 weeks	Midline prosencephalic development	Septo-optic dysplasia	<i>HESX1, SOX2, SOX3, OTX2</i>
7–20 weeks	Development of corpus callosum	Dysgenesis of corpus callosum	
2–4 months	Neuronal proliferation and differentiation	Microcephaly Megalencephaly Hemimegalencephaly Focal cortical dysplasia, type 2 Congenital neoplasias	<i>MCPH1, ASPM, SLC25A19, TSC1</i>
3–5 months	Neuronal migration	Lissencephaly/subcortical band heterotopia Cobblestone complex Neuronal heterotopias	<i>LIS1, DCX (XLIS), ARX, RELN, TUBA1A, FCMD, FKRP, LARGE, POMGnT1, FCMD (Fukutin), MEB, POMT1, FLNA (FLN1)</i>
gestational month 5 to postnatal years	Cortical organization	Polymicrogyria Focal cortical dysplasia, types 1 and 3 Schizencephaly	<i>GPR56, WDR62, SRPX2, PAX6, EMX2</i>
Development of the brainstem and cerebellum			
4–5 weeks	Midbrain–hindbrain patterning	Joubert syndrome and related disorders	
gestational week 5–postnatal month 7	Rhombic lip development and neuronal proliferation	Rhombencephalosynapsis Cerebellar hypoplasias Pontocerebellar hypoplasias	<i>TSEN54, RARS2, CLAM, VRK1</i>
gestational month 2–postnatal month 20	Migration and differentiation of cerebellar neurons	Lhermitte-Duclos disease	<i>PTEN</i>

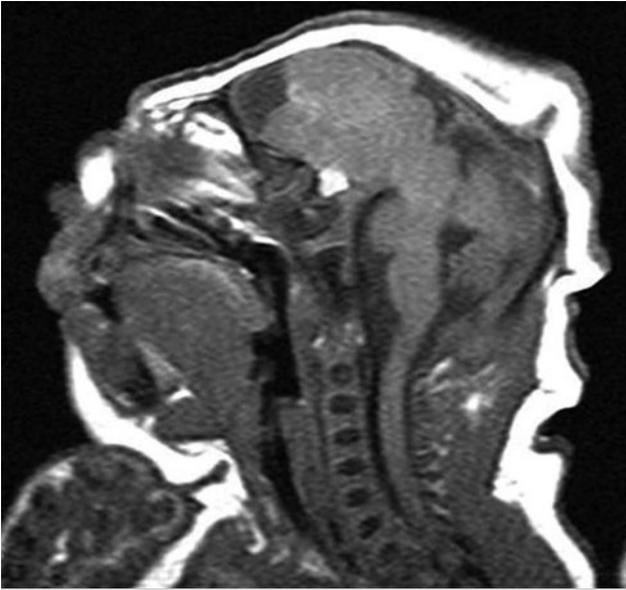


Fig. 15.1 Sagittal T1-weighted magnetic resonance image of a neonate born with anencephaly. All of the occipital and parietal lobes and most of the frontal lobes are degenerated. The posterior fossa structures are nearly intact. Note the proptotic eye and recessed forehead.

and Dandy-Walker malformations, as well as cleft lip, cleft palate, hypertelorism, microphthalmia, anophthalmia, syndactyly, and heart defects. Surgical options must be discussed in this context.

15.1.3 Congenital Dermal Sinus

A dermal sinus is a tract lined by keratinized squamous epithelium originating from a skin dimple with variable intracranial or intraspinal extension. It results from a focal adhesion and incomplete dissolution of the continuity between the neural and cutaneous ectoderm during neurulation, around the fourth week of gestation.^{9,10} The persistent tract can occur anywhere between the columella of the nose and the coccyx. Nearly all reported cranial cases occur in the midline and most commonly involve the external occipital protuberance (85%) and less often the nasion (10%) and the posterior parietal area (5%). Inclusion cysts (dermoid cyst, epidermoid cyst, and teratoma) may exist at any point along the tract.^{11–13} Dermal sinuses can connect the skin surface to any depth within the CNS and thus can be a source of intracranial infections and should be excised.¹⁴

15.1.4 Holoprosencephaly

Holoprosencephaly (HPE) is the most common developmental disorder of the human forebrain and is the result of failure of the forebrain to divide into two distinct hemispheres. Although it occurs once in every 250 conceptuses, most of these do not survive to term, and HPE is seen in only 1 in 10,000 live births and stillbirths.^{15,16} Few such newborns

survive past 1 year.¹⁷ HPE appears to be more common in girls, nonwhite races, and multiple-gestation pregnancies. Newborns with HPE often have a low birth weight. Genetic and environmental causes of HPE are thought to disrupt the prechordal plate during early gastrulation and the neural plate during neurulation.^{15,18} Perturbation of the prechordal mesoderm disrupts neural induction and regional patterning, both of which are critical to normal forebrain and midface development. Nonsyndromic, nongenetic causes are not common, and implicated teratogens include maternal diabetes, ethanol, antiepileptic drugs, retinoic acid, cigarette smoking, congenital cytomegalovirus infection, and alkaloids of the plant *Veratrum californicum*.^{19–21}

More than a third of patients with HPE have chromosomal number abnormalities, particularly trisomy 13, followed by trisomy 18 and triploidy, as well as certain malformation syndromes, such as Smith-Lemli-Opitz syndrome.^{22,23} Transmission can be autosomal-dominant, autosomal-recessive, or X-linked. The primary pathway implicated in HPE and other midline defects is the Sonic Hedgehog (SHH) signaling pathway.²⁴ Inheritance of HPE exhibits an 80% penetrance, most commonly related to several genes, including *SHH* on 7q36, *ZIC2* on 13q32, *SIX3* on 2p21, and *TGIF* on 18p11.3.²⁴ Less common genes implicated include *GLI2* on 2q14 and *NODAL* on 10q22.11. Disrupted gradients of gene expression along the three anatomical axes are thought to be elementary in the pathogenesis of HPE. Variations in the timing and location of gene mutations help to account for the diverse phenotypic spectrum in those affected by HPE. The genetics of HPE is thought to be a complex, multiple-hit process because a genetic mutation cannot be identified in up to 83% of HPE cases, although the increasing use of aCGH is beginning to change the landscape.^{15,24}

The classification put forth by DeMyer and colleagues in the 1960s still serves as a useful starting point in understanding this heterogeneous disease.²⁵ The most severe form, alobar HPE, is characterized by an almost complete lack of midline cleavage between the hemispheres, resulting in the classic “monovertricle” of the forebrain (► Fig. 15.3). This single ventricle is often associated with a dorsal cyst, and there is no identifiable corpus callosum or interhemispheric fissure. Semilobar HPE forms when there is some separation of the posterior hemispheres and occipital horns but the anterior hemispheres and associated ventricles fail to separate. Most of the corpus callosum fails to develop, except for the splenium. The least severe form of classic HPE is the lobar type, in which the lack of midline cleavage is restricted to the rostral–ventral forebrain with near-normal separation of the remainder of the forebrain. The corpus callosum is normal with the exception of the genu. A more recently recognized and milder subtype of HPE, known as the middle interhemispheric variant, results from the failed separation of the posterior frontal and parietal lobes but spares the rostral–ventral frontal area.^{17,26}

Superimposed on the different forms of HPE described above is variability in the cleavage of the deep gray nuclei.²⁷ In every case of HPE, there is some degree of hypothalamic noncleavage. The next most likely deep gray structures not to cleave are the caudate nuclei, followed by the lentiform nuclei and finally the thalami, which remain fused in 67% of patients. The extent of fusion of these deep gray nuclei, particularly the

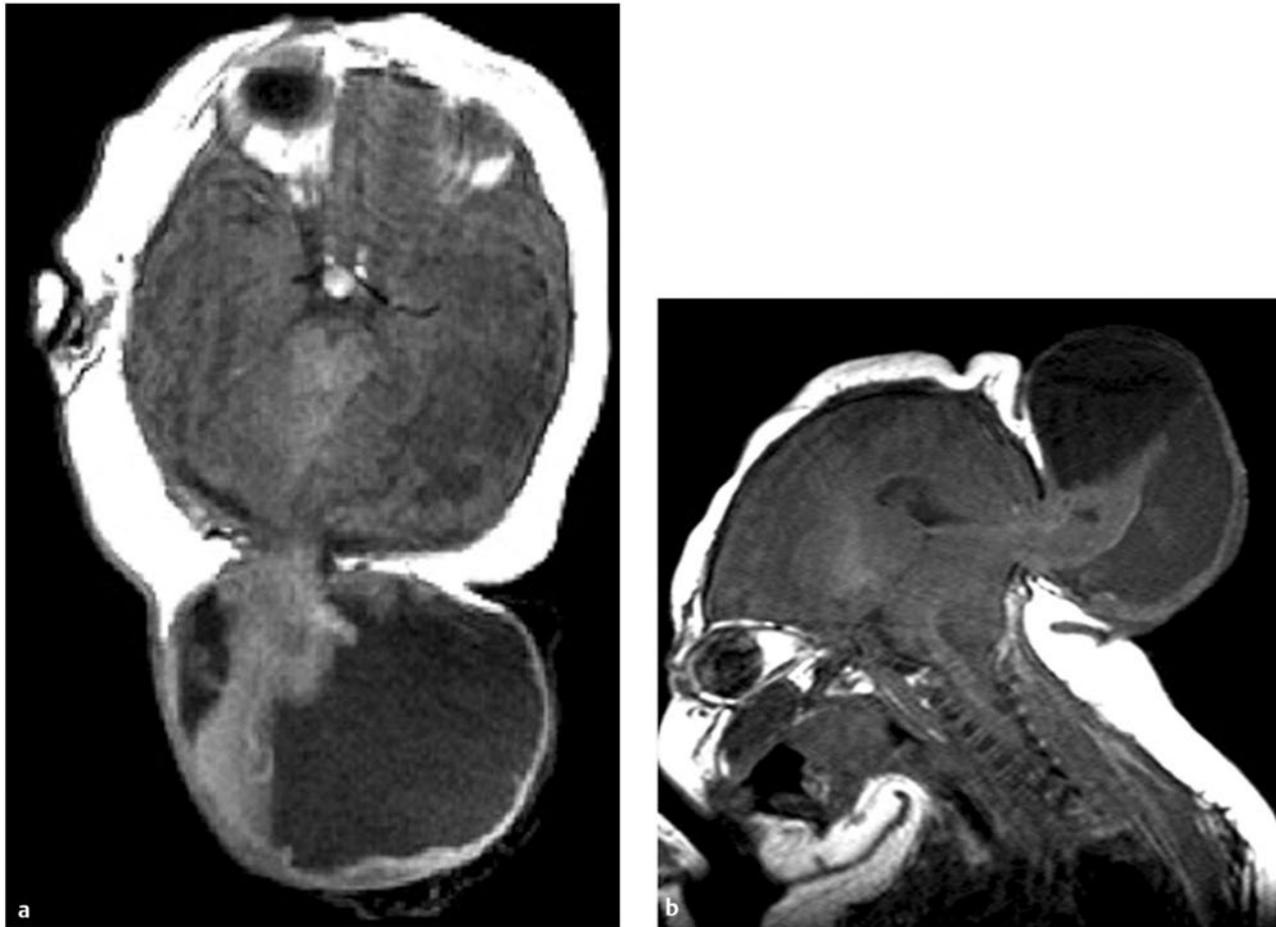


Fig. 15.2 Axial T1-weighted (a) and sagittal T1 weighted (b) magnetic resonance images of a newborn with occipital cephalocele show suboccipital cranial defect and herniated cerebellum.

basal ganglia and thalami, is proportional to the hemispheric noncleavage described by DeMyer and has prognostic value for neurologic outcome.²⁸ However, there are noted exceptions to this trend, which may in part account for the variation in the severity of neurologic dysfunction among patients with the same type of HPE under DeMyer's classification. The variability of morphologic nonseparation and phenotypic expression of HPE precludes a simple and accurate prognosis for each patient.

It has long been observed that the “face predicts the brain.” In other words, the various forms of midface hypoplasia often associated with HPE serve as markers of the underlying fore-brain abnormalities.²⁹ Severe midface abnormalities, such as cyclopia, ethmocephaly, and cebocephaly, often coincide with alobar HPE.^{18,30} Other associated midline abnormalities can be relatively subtle and include arhinencephalia, agenesis of the corpus callosum, pituitary abnormalities, median cleft lip, and the presence of a single maxillary central incisor.³¹ Clinically, patients can present with oral motor dysfunction, seizures, endocrinopathies (especially diabetes insipidus), microcephaly, hydrocephalus, dystonia, spasticity, choreoathetosis,

and developmental delay. The hydrocephalus and third ventricular dorsal cyst of alobar HPE are related to blockage of the outlet of the third ventricle in conjunction with aqueductal stenosis.²²

15.1.5 Hydranencephaly

Hydranencephaly results from destruction of a previously normally developing brain by in utero vascular occlusions and hemorrhages, infection, or maternal exposure to drugs, cigarette smoking, or radiation.³² The hemispheres corresponding to the middle cerebral artery or, more often, the entire anterior circulation is resorbed and replaced with cerebrospinal fluid (► Fig. 15.4). The thalamus, brainstem, and cerebellum are spared along with the meningeal sac and falx. There may be a small residual occipital, frontal, or temporal cortex present. Hydranencephaly, which appears on imaging as nearly complete absence of the cerebral hemispheres, can be difficult to differentiate from HPE with hydrocephalus. The presence of a falx and separate thalami, along with the absence of facial anomalies and the frontal cortical mantle, distinguishes hydranencephaly from HPE.

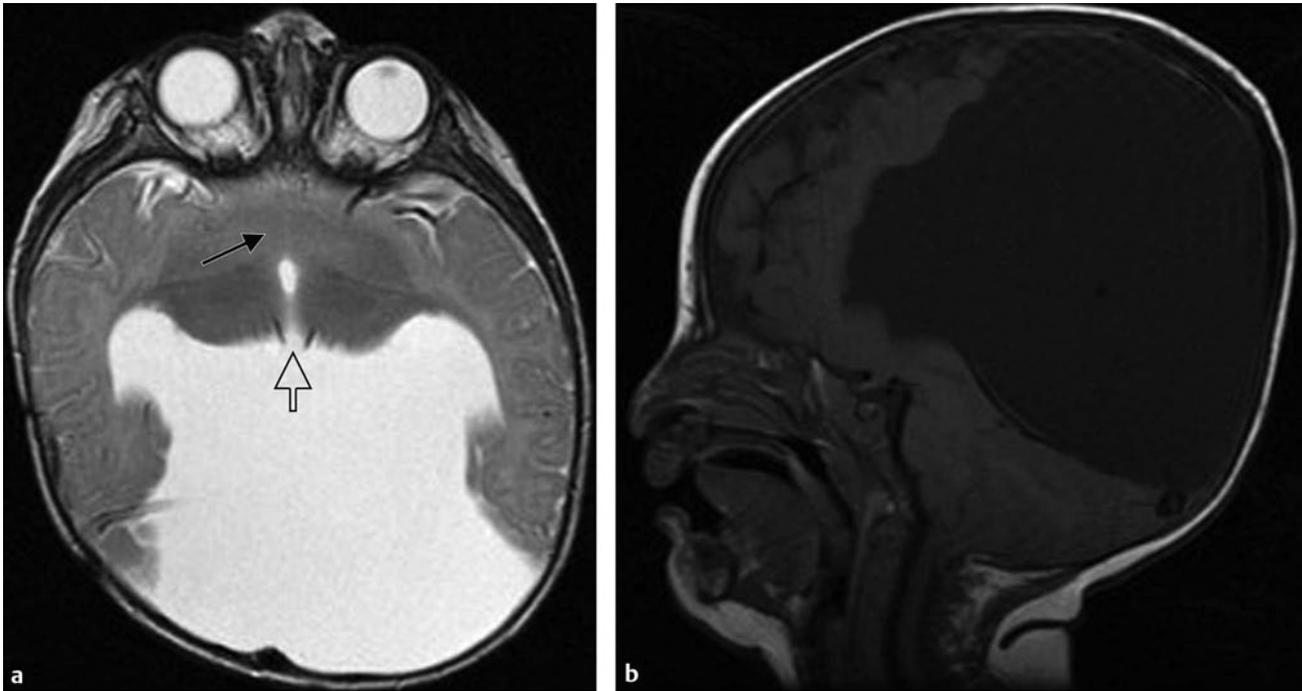


Fig. 15.3 Axial T2-weighted (a) and sagittal T1-weighted (b) magnetic resonance images of a child with alobar holoprosencephaly show fused basal ganglia (arrow) and a monoventricle that opens to a dorsal cyst. The thalami are partially fused (open arrow).

15.1.6 Septo-optic Dysplasia

Septo-optic dysplasia (SOD), named by de Morsier in 1956, is a disorder defined by any combination of the classic triad of optic nerve hypoplasia, pituitary dysfunction, and midline brain defects, particularly absence of the septum pellucidum (► Fig. 15.5). There is considerable variation in the phenotype, with fewer than a third of patients having all of the manifestations³³; however, all patients have optic nerve hypoplasia, although the degree of visual impairment and nystagmus is variable. Approximately one-half to two-thirds of patients have an endocrinopathy. Of these, almost all have dysplasia of the hypothalamic–pituitary axis, including a truncated or absent pituitary stalk, a hypoplastic anterior pituitary lobe, and an ectopic or absent posterior pituitary gland.³⁴ Pituitary hormone insufficiency is more frequent in those missing a septum pellucidum than in those with an intact septum. Most patients with SOD are of normal intelligence, but those with developmental delay often have additional brain malformations, including cortical dysplasia and schizencephaly, and they are diagnosed as having SOD+.^{35,36} However, when schizencephaly or polymicrogyria is present, the child typically has minimal or no pituitary dysfunction.³⁷

The management of children with SOD includes the early detection and replacement of deficient pituitary hormones. Although the etiology of SOD remains unclear, maternal diabetes mellitus, cytomegalovirus infection, and exposure to toxins and mutations in four key genes have been implicated: *HESX1*, *SOX2*, *SOX3*, and *OTX2*. Abnormalities in the interplay between these key regulators at the prechiasmatic plate during development determine, in part, the severity of midline brain maldevelopment.³⁸

15.1.7 Dysgenesis of the Corpus Callosum

Agenesis of the corpus callosum (ACC), like SOD and HPE, is a disorder of midline development. It occurs commonly, affecting 0.7% of the general population and 2.3% of the developmentally disabled population.^{39,40} It has a prevalence of between 1 in 4,000 and 1 in 5,000 live births.⁴¹ It can occur in isolation or concurrently with other CNS malformations and is a feature in more than 20 malformation syndromes (see box “Disorders Associated with Agenesis of the Corpus Callosum (p.175)”). In all circumstances, the common pathogenesis is the failure of cortical cells to grow axons across the midline. Failure to develop the dorsal portion of the rostral wall of the midline prosencephalon starting in the middle of the second month of gestation prevents the formation of the commissural plate through which callosal fibers cross the midline. Axons that would normally form the corpus callosum are diverted, forming longitudinal bundles of Probst in a location superior and medial to the lateral ventricles (see box “Magnetic Resonance Imaging Findings of Agenesis of the Corpus Callosum (p.177)”).⁴² Disruption of the migration and differentiation of callosal neurons, impairment of the molecular control of axon growth (e.g., DCC and L1 adhesion molecule), or loss of the guidance of axons traversing the midline by chemoattractants (e.g., netrin 1 and Slit protein) also lead to ACC, but Probst bundles are characteristically absent.⁴³ This often occurs in lissencephaly with ACC (e.g., Walker-Warburg syndrome).

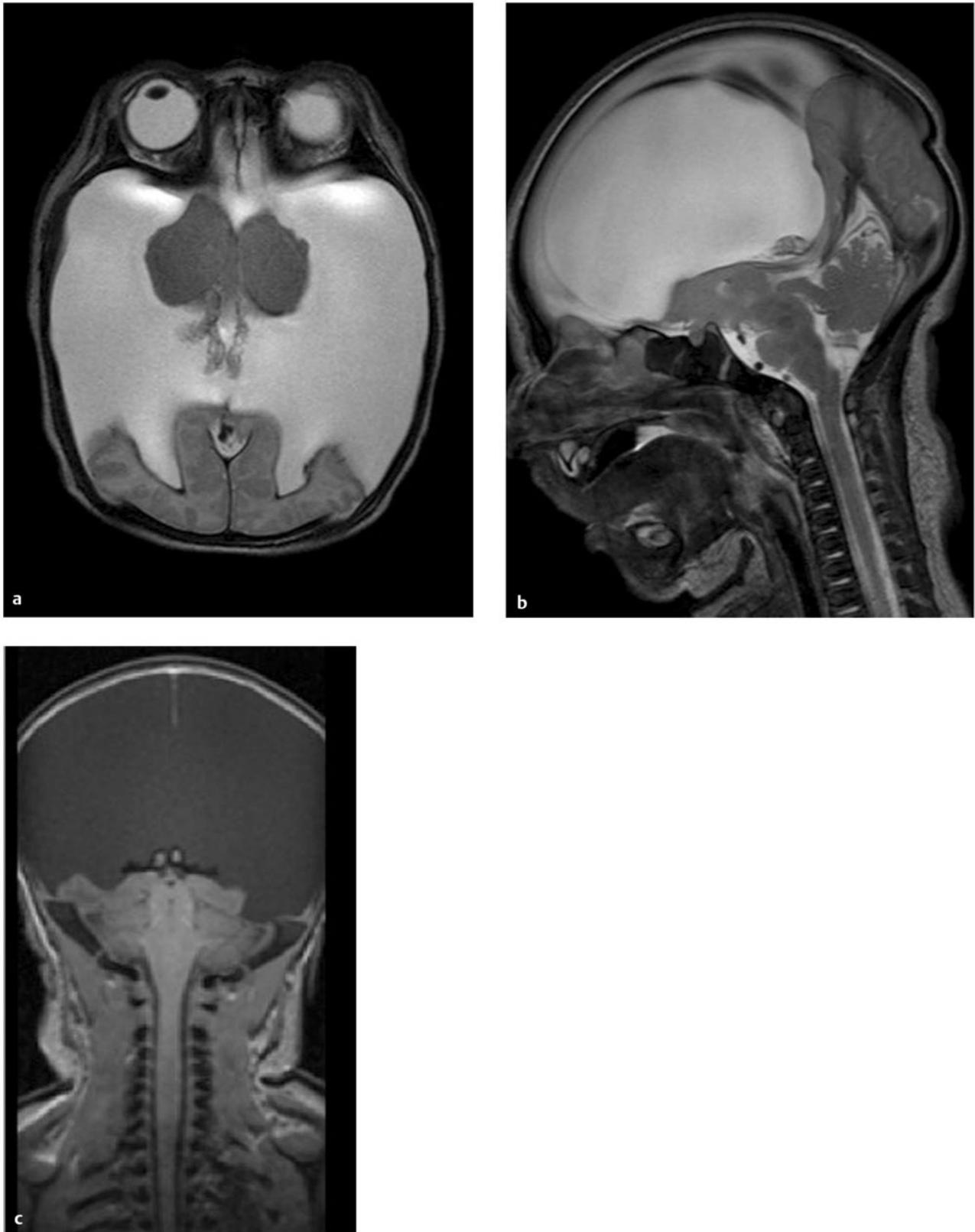


Fig. 15.4 Gradient-echo axial (a) and sagittal T2-weighted (b) and coronal T1-weighted (c) magnetic resonance images of child with hydranencephaly. The cerebral hemispheres, except for a thin rim of the occipital cortex, are absent and replaced by cerebrospinal fluid. The thalamus, brainstem, and cerebellum are preserved. Unlike in HPE, the falx is fully formed.

Disorders Associated with Agenesis of the Corpus Callosum

- Always present
 - Aicardi syndrome
 - Andermann syndrome
 - L1 disease
 - Mowat-Wilson syndrome
 - Chiari type 2 malformation
- Occasionally present
 - Holoprosencephaly
 - Septo-optic dysplasia
 - Dandy-Walker malformation
 - Lissencephaly (Walker-Warburg syndrome, Miller-Dieker syndrome)
 - Other disorders of neuronal migration
 - Fetal alcohol syndrome
 - Metabolic disorders
 - Trisomies 8, 13, and 18

Magnetic Resonance Imaging Findings of Agenesis of the Corpus Callosum

- Separation and parallel orientation of the lateral ventricles
- Radial orientation of the interhemispheric gyri
- Colpocephaly (dilated occipital ventricular horns)
- Probst bundles
- Inversion of the hippocampi
- Absent septum pellucidum
- Rostral extension of the third ventricle
- Hypoplastic or enlarged anterior commissure
- Azygous or wandering anterior cerebral artery
- Absent cingulate sulci with everted cingulate gyri

In partial ACC, the commissural plate is formed, but an arrest of the developing commissure between weeks 7 and 20 of gestation results in an incomplete corpus callosum⁴⁴ (► Fig. 15.6). Typically, the posterior body, splenium, inferior genu, and rostrum of the corpus callosum are missing because they are thought to develop last. However, dysgenesis of the anterior body, genu, and rostrum with a normal splenium has been observed, particularly with semilobar HPE.⁴⁵ This finding suggests that the growth of the corpus callosum is bidirectional instead of anterior to posterior, as has been widely accepted in the past. Lipomas, arising from the remnant of the meninx primitiva, can also prevent full growth of the corpus callosum by mechanical obstruction of the crossing axons.^{46,47}

ACC can sometimes be accompanied by interhemispheric cysts. Barkovich et al classified the cysts as type 1 if they communicate with the lateral or third ventricle and as type 2 if they do not.⁴⁸ They are further divided depending on whether they are associated with hydrocephalus and/or other cerebral abnormalities, such as diencephalic malformation, heterotopia, and polymicrogyria. Except for the subgroup associated with Aicardi syndrome, ACC with interhemispheric cysts is seen predominantly in boys. The cysts are thought likely to be arachnoid, ependymal, or neuroepithelial, but their cause is still indeterminate.



Fig. 15.5 Coronal T1-weighted magnetic resonance image of septo-optic dysplasia shows absence of the septum pellucidum and a hypoplastic optic chiasm (arrow). The frontal horns of the lateral ventricles have a characteristic horizontal roof.

Most children with isolated dysgenesis of the corpus callosum have only subtle neuropsychological deficits because of compensation by the anterior and hippocampal commissures, strengthening of the ipsilateral tracts, and possible bilateral representation of functions.^{41,44} Approximately 15% of patients with isolated ACC have cognitive deficits and psychological disorders, in addition to seizures and hydrocephalus. The morbidity of ACC is related to the associated intracranial anomalies and genetic syndromes.^{47,49}

15.1.8 Microcephaly

Microcephaly is a clinical finding defined as a head circumference that is 2 or more standard deviations below the age- and sex-matched mean. Children with microcephaly do not have true dysmorphic facial features, but the small cranium creates the appearance of a sloping forehead and prominent ears. The small head reflects an undersized brain with a decreased number of neurons related to a decreased number of neural progenitors, decreased proliferation of neurons, or excess death of the progenitors and neurons.^{50,51} Environmental causes include congenital infections (e.g., rubella and cytomegalovirus infection); intrauterine exposure to teratogens (e.g., irradiation, alcohol, and cocaine); and intrauterine growth restriction. Microcephaly is also a feature of many other brain malformations, such as lissencephaly and HPE, and of metabolic disorders. When secondary causes of microcephaly and the presence of other cerebral and extracerebral malformations are excluded, the children are then described as having either microcephaly vera (MV) or microcephaly

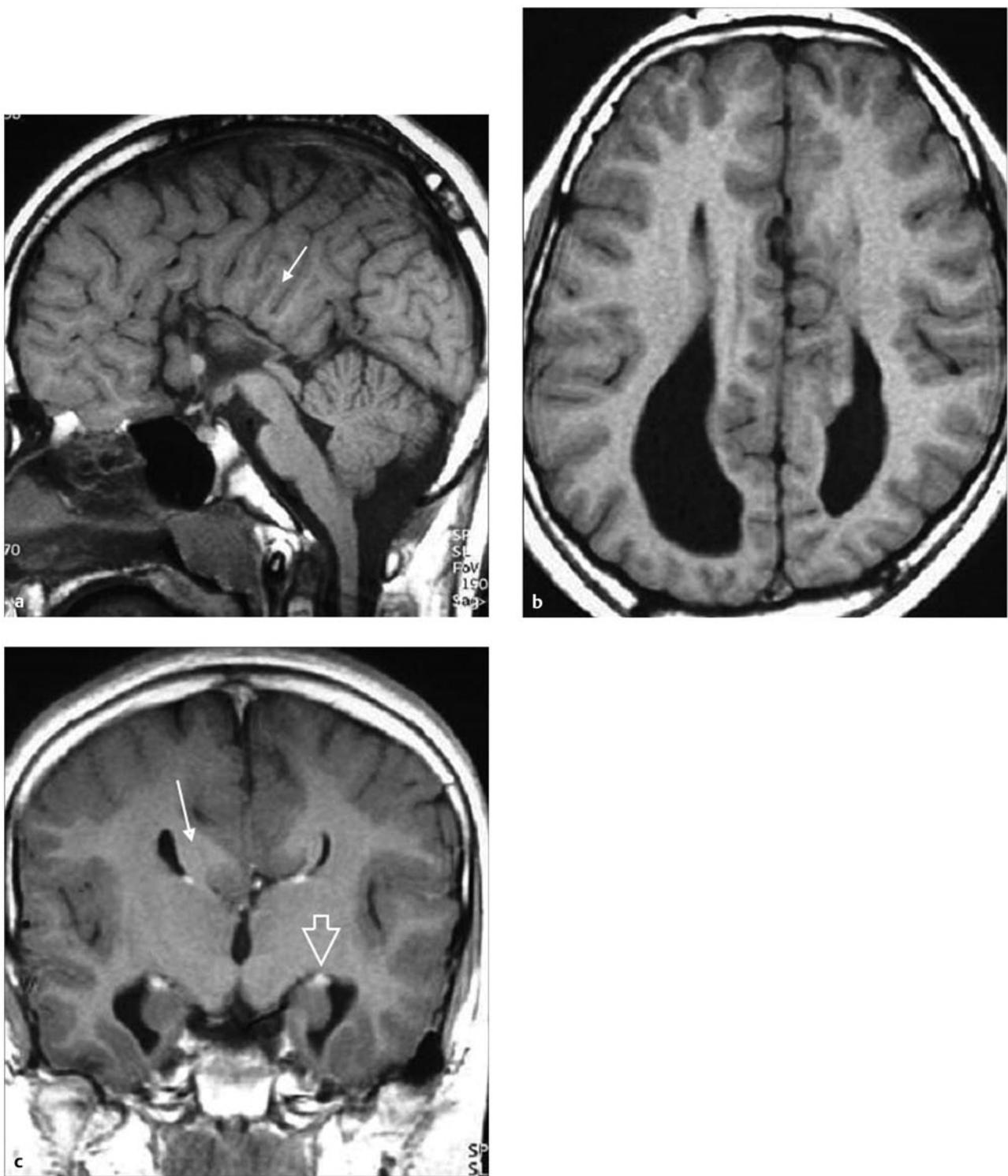


Fig. 15.6 Dysgenesis of the corpus callosum. (a) Midsagittal T1-weighted magnetic resonance (MR) image shows absence of the body, splenium, and rostrum of the corpus callosum. The interhemispheric gyri are oriented radially (*arrow*). (b) Axial T1-weighted MR image shows widely separated and parallel lateral ventricles. The frontal horns are pointed and the occipital horns dilated (colpocephaly). (c) Coronal T1-weighted MR image shows agenesis of the corpus callosum and Probst bundle (*arrow*) indenting the medial surface of the lateral ventricles, resembling a “moose head.” Associated malformations include vertical orientation of the hippocampus (*open arrow*) and distortion of the temporal horn.

with simplified gyral pattern (MSG). The two likely represent a continuous phenotype.

In MV, or “true” microcephaly, the small brain has a normal gyral pattern. The cortical mantle has the normal six layers, but it can be reduced in thickness, with a depletion of neurons in layers 2 and 3.^{50,51} MV has been attributed to faulty proliferation in the germinal zone before the 26th week of gestation, leading to exhaustion of the neuronal pool.⁵² Defects at multiple chromosomal loci, including the genes *MCPH1*, *ASPM* (*MCPH5*), and *SLC25A19*, have been identified and are transmitted in an autosomal-recessive manner.⁵¹ These children have intellectual disability that varies from mild to moderate. Seizures are uncommon, and the life span of patients with mild cases is often normal.

MSG carries a worse prognosis than MV. The child invariably has neonatal seizures, has moderate to severe intellectual disability, and often develops diffuse spasticity.^{53,54} Severe forms of MSG are lethal in infancy. Pathologic findings include a simplified gyral formation, but unlike in lissencephaly, the cortex is not thickened and has normal lamination. When thickening and dyslamination of the cortex are present, the diagnosis of microlissencephaly is given.⁵⁵ MSG and microlissencephaly are possibly the result of a disruption of migration, as well as abnormal proliferation. Like MV, MSG is probably caused by defects of multiple genes transmitted in an autosomal-recessive manner.

15.1.9 Megalencephaly

Megalencephaly is defined as a brain volume greater than 2 standard deviations above the mean. Some authors suggest stricter criteria and include only patients with an occipito-frontal head circumference exceeding the mean by 2.5 standard deviations or the 98th percentile curve by 1 cm or more, but with normal ventricles and extracerebral space.⁵⁶ Depending on the etiology, megalencephaly is described as anatomical or metabolic and is easily differentiated by the history and physical examination. Children with metabolic megalencephaly are born with a normal head circumference, which rapidly increases in girth during infancy from the brain cells' accumulation of undegraded metabolic substrates or aberrant myelin due to a lysosomal deficiency or a dysmyelination syndrome.⁵⁷ Consequently, the children develop progressive neurologic deterioration with signs and symptoms of elevated intracranial pressure (ICP). A thorough family history often reveals autosomal-recessive or X-linked-recessive inheritance.⁵⁸ Examples of causes of metabolic megalencephaly are the gangliosidoses, mucopolysaccharidoses, sphingolipidoses, maple syrup urine disease, Alexander disease, and Canavan disease.

On the other hand, children with anatomical megalencephaly have normal ICP. The girth of the head, which may already be enlarged at birth, increases rapidly within first few months of life and then runs above, but parallel to, the 98th percentile curve.⁵⁸ Almost all anatomical megalencephalies are inherited in an autosomal-dominant pattern. Some patients will have cutaneous stigmata and dysmorphic features consistent with certain neurocutaneous syndromes (e.g., neurofibromatosis and tuberous sclerosis) or rare growth disturbance disorders (e.g., achondroplasia).⁵⁶ Cases without an

etiology or associated syndrome are called primary or familial megalencephaly. These children have normal intelligence and neurologic examinations, and they often have relatives with large heads who are otherwise also normal.⁵⁹ Although all the megalencephalies are classified by Barkovich et al as disorders of the proliferation of normal cells, there are no reported histologic studies of primary megalencephaly, and its embryogenesis is not known.⁶⁰ Previous reports describing intellectual disability, epilepsy, paresis, and the presence of large cortical cells could be due to the grouping of all causes of megalencephaly together and confusion with hemimegalencephaly.^{56–58,61}

15.1.10 Hemimegalencephaly

The clinical findings and prognoses of hemimegalencephaly are notably different from those of megalencephaly. There is marked asymmetry of the hemispheres in hemimegalencephaly, with the affected side enlarged and the opposite side slightly smaller than normal, resulting in varying degrees of midline shift (► Fig. 15.7). Occasionally, the ipsilateral cerebellum and brainstem are also increased in volume.⁶² Computed tomography (CT) and magnetic resonance (MR) imaging show ventriculomegaly with straightening of the frontal horns and colpocephaly in the affected hemisphere (► Fig. 15.8).⁶³ The cerebrum is often lissencephalic, but polymicrogyria, gray matter heterotopia, focal cortical dysplasias, and rarely

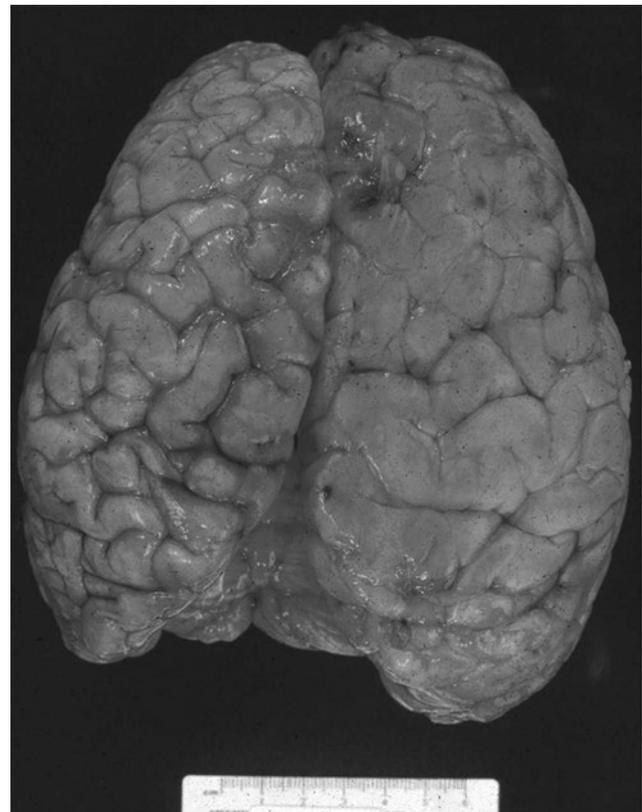


Fig. 15.7 Vertex view of the gross pathology of hemimegalencephaly. The entire right hemisphere is enlarged and has pachygyria and shallow sulci.



Fig. 15.8 Axial T1-weighted image of a child with hemimegalencephaly. The overgrown right hemisphere has an enlarged lateral ventricle, thickened cortex with a poor gray–white matter junction, and primitive veins in the sylvian fissure (*arrow*). There is diffuse loss of sulci in both hemispheres.

schizencephaly and ACC may also be seen. The cortex is thickened and is indistinct from the underlying white matter, which is often hyperintense on a T2-weighted MR image.

Histologic examination of the corresponding cerebrum reveals disruption of cortical lamination, a poor gray–white matter border, and abundant hypertrophic neurons and balloon cells positioned throughout the gray and white matter.⁶⁴ Both cell types are immunoreactive to glial and/or neuronal proteins. Many authors have concluded that hemimegalencephaly is a disorder of cellular lineage, neuronal migration, and/or genetic regulation of body symmetry.^{63,65} However, the etiology is still uncertain, and there is no known genetic mutation or familial inheritance. Hemimegalencephaly with neurocutaneous disorders has a similar neurologic picture, pathologic features, MR imaging findings, and electroencephalographic abnormalities.⁶³

The child with hemimegalencephaly typically presents with cranial asymmetry, hemiplegia, and intractable seizures that start soon after birth. Partial seizures occur most frequently, followed by tonic seizures and infantile spasms.⁶³ The best chance for seizure control and improvement of neurologic and psychomotor development is with early hemispherectomy or hemispherotomy.⁶⁴ Children with the early onset of neurologic symptoms demonstrate severe retardation of global development and an increased risk for mortality during infancy.⁶³ At the other end of the spectrum, those with mild hemimegalencephaly may have only subtle deficits and a normal life expectancy.

15.1.11 Focal Cortical Dysplasia

Focal cortical dysplasias (FCDs) are localized areas of malformed cerebral cortex that are frequently associated with epilepsy. Taylor et al were the first to describe FCDs and their association with nonfamilial, nonsyndromic refractory epilepsy.⁶⁶ A broad spectrum of histopathology is seen in the diagnosis of FCD. Currently, a three-tiered classification system is used to characterize specific clinicopathologic FCDs.⁶⁷ Type 1 FCDs are isolated lesions that present as radial (FCD type 1a) or tangential (FCD type 1b) dyslamination of the neocortex, microscopically identified in one or multiple lobes. Type 2 FCD is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (type 2a) or with (type 2b) balloon cells. Type 3 FCD occurs in combination with hippocampal sclerosis (FCD type 3a) or epilepsy-associated tumors (FCD type 3b), or adjacent to vascular malformations (type 3c) or epileptogenic lesions acquired in early life (type 3d), such as traumatic injury, ischemic injury, and encephalitis. The dysplasias can be localized to any part of the cerebrum but are frequently found at the frontal and temporal lobes.⁶⁸

Type 2 FCD, with or without balloon cells, is usually visible on MR imaging, is highly epileptogenic, and has the lowest operative success rate. MR imaging findings include cortical thickening, poor delineation of the gray–white matter junction, and increased signal of the cortex and underlying white matter.⁶⁹ Type 1 FCD is typically not visible on MR imaging but has better surgical outcomes than lesions with dysmorphic neurons.⁷⁰ Besides the histologic composition, the seizure-free success rate is determined by the extent of resection.

The pathogenesis of FCD is not clear but may occur during cell proliferation, neuroblast migration and differentiation, and/or cortical organization.⁶⁸ The tubers of tuberous sclerosis and cortices of hemimegalencephaly also contain balloon cells and are thus often grouped together with FCD.⁷¹

15.1.12 Congenital Neoplasms

Even though congenital neoplasms are classified under the heading of abnormal proliferation, their etiology is likely multifactorial, as is the case with postnatal-onset tumors. Particular to the developing brain, however, is its susceptibility to neoplastic transformation by genetic mutation and teratogens because of rapid cellular proliferation.⁷² Alterations of the regulatory cues for cell proliferation, differentiation, and apoptosis have the potential to result in neoplastic growth because many oncogenes and tumor suppressor genes involved in cancers are also regulators of normal CNS development.^{73,74} The finding of increased risk for pediatric brain tumors when there is a maternal family history of birth defects suggests either that malformations and neoplasia share a common etiology or that malformations confer a susceptibility for neoplastic transformation during childhood.^{75,76} Yachnis et al found that the granule cells that comprise vermian dysplasias are mitotically active after birth.⁷⁷ These granule cells are therefore potential precursors of cerebellar tumors. Pediatric supratentorial tumors (e.g., ganglioglioma, dysembryoplastic neuroepithelial tumor, and pleomorphic xanthoastrocytoma) have also been linked to, or have been observed to develop from, cortical dysplasias.^{78–81}

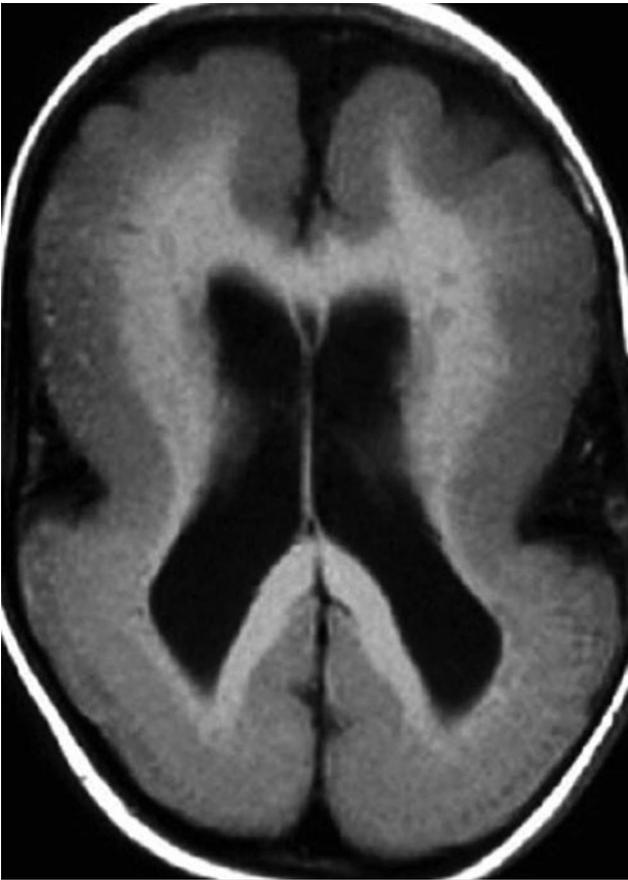


Fig. 15.9 Axial T1-weighted magnetic resonance image of classic lissencephaly (type 1) shows a smooth cortical surface with minimal gyri and sulci at the frontal lobes. The shallow sylvian fissures give the brain an "hourglass" configuration.

15.1.13 Lissencephaly

Lissencephaly is a diffuse bihemispheric abnormality that occurs in approximately 12 of every 1 million births and is characterized by a smooth or nearly smooth cortical surface (► Fig. 15.9).^{39,82} It is a disorder of neuronal migration, ranging in severity from the complete absence of convolutions (agyria) to a regional decrease in sulcation resulting in broad gyri (pachygyria). Lissencephaly is characterized by a cerebral cortex that is thickened to 10 to 20 mm (normal is 2.5 to 4 mm) and has four layers instead of six.^{83,84} Subcortical band heterotopia (SBH) is considered a mild form of lissencephaly in which bands of gray matter of varying width become embedded in the white matter and parallel the cortex of both hemispheres (► Fig. 15.10).

Lissencephaly can be classified genetically on the basis of genes involved in neuronal migration that, when mutated, result in lissencephaly. Classic lissencephaly (previously described as type 1) is associated with deletions of the *LIS1* gene on chromosome 17p13 and the *DCX* (also known as *XLIS*) gene on chromosome Xq.^{85,86} Both genes regulate microtubule formation and activity during neuronal migration. The tubulin- α 1a gene (*TUBA1A*), like *LIS1* and *DCX*, encodes a microtubule-related protein and has recently been implicated in the pathogenesis of

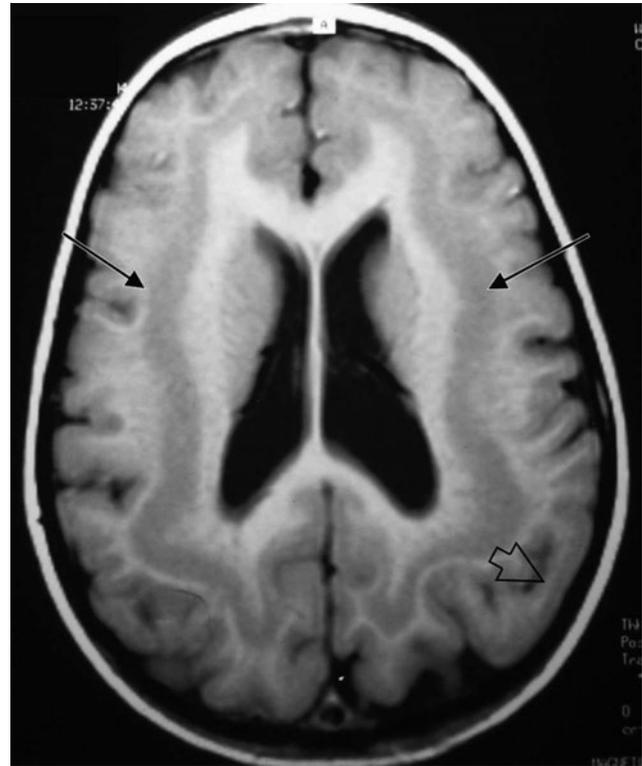


Fig. 15.10 Axial T1-weighted magnetic resonance image of a child with subcortical band heterotopia (double cortex). The bands of gray matter are situated between the lateral ventricles and cerebral cortex (arrows). Note the associated pachygyria (open arrow).

lissencephaly.⁸⁶ Large deletions of *LIS1* and the contiguous gene *14-3-3 ϵ* are associated with Miller-Dieker syndrome, which is characterized by lissencephaly with dysmorphic facial features.^{39,82} Patients with classic lissencephaly, on the other hand, have no other abnormalities, including those of the face. Mutations of *DCX* also cause isolated lissencephaly in males, but heterozygous females develop SBH.⁸³ The frontal lobes of patients with *DCX* mutations are affected more than the occipital lobes, and the opposite is true in patients with *LIS1* mutations.

Lissencephaly plus ACC occurs with mutation of the *ARX* gene located on chromosome Xp22.13 and is associated with underdevelopment of the genitalia.⁸³ Patients who have lissencephaly with mutations of the *RELN* gene manifest malformations of the hippocampus and a severely hypoplastic cerebellum.⁸³ Little is known about the genetics of microlissencephaly, which is characterized by a severely microcephalic brain with diffuse decreased sulci and cerebellar hypoplasia.⁵⁴

Children with classic lissencephaly have a normal head size at birth, but their head growth plateaus, resulting in microcephaly within the first year.⁸² They are often intellectually disabled, have early-onset seizures, and exhibit hypotonia that shifts to hypertonia. The age at onset, severity of seizures, and degree of cognitive dysfunction depend upon the lobes of the brain involved and the volume and extent of misplaced gray matter.⁸² Treatment entails providing adequate nutrition, managing aspiration episodes, and controlling seizures. The majority of patients die within 10 years of aspiration pneumonia and sepsis.

15.1.14 Cobblestone Complex

Cobblestone dysplasia is a disorder of glycosylation that results in cortical dysplasia and dysmyelination, dysplastic cerebellum with cysts, and brainstem hypoplasia.⁸⁷ Previously classified as lissencephaly type 2, because of the grossly smooth surface of the involved cortex, cobblestone dysplasia has now been re-categorized since its mechanism of malformation was elucidated. In contrast to lissencephaly, in which the neurons fail to reach the cortical plate, in cobblestone dysplasia, the neurons pass through the cortex into the subpial space and appear on the brain surface like cobblestones.^{83,87} The cortex is thick, as it is in lissencephaly, but cortical lamination is not evident. Moore et al discovered that failure to glycosylate the dystroglycan results in breaches in the glia limitans, the pial surface lamina, allowing migrating neurons to exit the brain proper.⁸⁸

Loss of dystroglycan function may underlie the cobblestone dysplasia observed in at least three genetic disorders: Walker-Warburg syndrome, Fukuyama-type congenital muscular dystrophy, and muscle–eye–brain disease.⁸⁹ Children born with these congenital muscular dystrophies have profound neonatal hypotonia, ophthalmologic malformations, and cerebellar dysplasia.⁸³ Patients may die at infancy or live to adulthood without significant morbidity depending on the severity of weakness, seizures, and intellectual disability and on the type of muscular dystrophy.

15.1.15 Gray Matter Heterotopia

Neuronal heterotopias are disorders of neuronal migration that result in collections of normal neurons situated anywhere between the germinal zones and the subcortical white matter.⁹⁰ Normal neural migration entails attachment of neurons to radial glial cells and migration along the glial cells, followed by detachment at the appropriate cortical layer. Interruption of this basic process along various points results in the heterogeneous appearances of the neuronal heterotopias.⁸³ Barkovich et al grouped heterotopias into three categories: periventricular (subependymal), subcortical (other than band heterotopia), and marginal glioneuronal heterotopia.⁶⁰

Periventricular heterotopia is characterized by nodular masses of gray matter lining the lateral ventricles and protruding into the ventricular spaces (► Fig. 15.11). Bilateral periventricular nodular heterotopia may be X-linked, and therefore familial, while unilateral subependymal heterotopia and sparsely scattered subependymal heterotopia present sporadically.⁹¹ When it is X-linked, bilateral periventricular nodular heterotopia is more prevalent in females because of its lethality in males. Bilateral periventricular nodular heterotopia results from a defect in the filamin A (also known as filamin-1) gene (*FLNA*), which is needed for linking actin filaments to glycoproteins and is essential to the process of neuronal migration.^{92,93} Ninety percent of these patients have epilepsy, and many have intractable seizures.³⁹ Females who are heterozygous for the mutation have epilepsy, which varies in severity, and have borderline to normal intelligence. Patients who have periventricular heterotopias are more likely to demonstrate normal development in comparison with those who have other types of heterotopia.

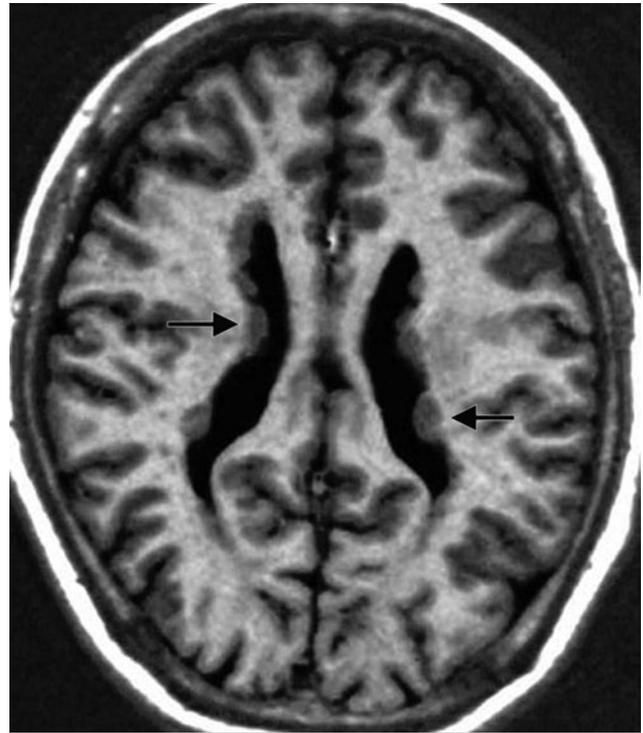


Fig. 15.11 Axial T1-weighted magnetic resonance image of bilateral periventricular nodular heterotopia shows gray matter lining and indenting the lateral ventricles (arrows).

Subcortical heterotopia has three different forms, each with its own pattern of ectopic tissue: multiple nodules, curvilinear ribbons, and a mixture of deep nodular regions with curvilinear areas in the periphery⁹⁴ (► Fig. 15.12). Patients with subcortical heterotopias have weakness, spasticity, hyperreflexia, and seizure onset within the first decade of life. Marginal glioneuronal heterotopia carries the worst prognosis of the three categories; patients have severe developmental delay, early onset of seizures, and a low survival rate past the age of 1 year.⁹⁵ The pathology shows neurons breaching the neuropial border and causing damage and fusion of the normal barriers between cortical convolutions.

Except for those with marginal glioneuronal heterotopia, most patients with heterotopia are asymptomatic and of normal intelligence. In general, larger masses of heterotopic tissue result in a more severe clinical picture.⁹⁶ In severe cases, patients can develop infantile spasms, Lennox-Gastaut syndrome, motor impairment, and intellectual disability. The management of neuronal heterotopias centers largely on control of seizures with antiepileptic drugs. Localized seizure foci that are refractory to medical management may be surgically removed if the seizure focus is amenable to resection. The preoperative imaging characteristics of heterotopia are subtle because the lesions do not enhance and are devoid of calcification.⁹⁷

15.1.16 Schizencephaly

Schizencephaly has often been described as a disorder of neuronal migration resulting in cerebral clefts. It is now

believed that the causes may be heterogeneous, with many cases secondary to vascular disruption.⁹⁰ However, unlike in cases of simple vascular occlusion, the walls of the clefts are lined by abnormal cortex that is typically polymicrogyric, and thus some authors have suggested that schizencephaly is a result of abnormal postmigrational development and should be reclassified as polymicrogyri of disruptive etiology (see box “Classification of Supratentorial Malformations (p.171)”).^{90,96} The defect, typically in the perisylvian region, runs the full thickness of the cortex, from the pial surface to

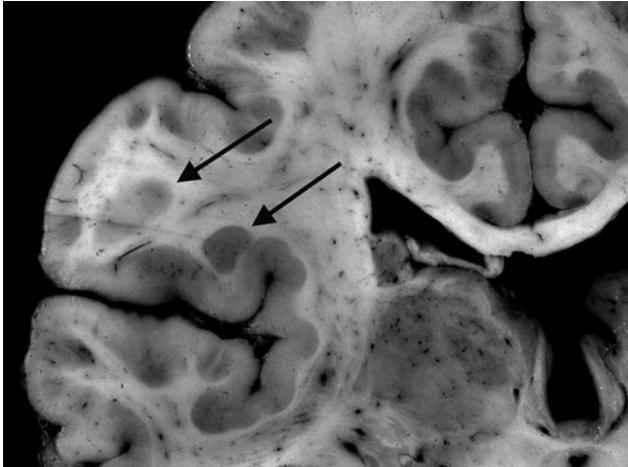


Fig. 15.12 Coronal gross pathology shows small subcortical gray matter heterotopias (arrows) at the frontal operculum with normal overlying cortex.

the ventricular surface, permitting direct communication between the lateral ventricle and the subarachnoid space (► Fig. 15.13). Gyri on the cerebral surface project radially from the cleft and usually contain cortical dysplasias. Schizencephaly is also frequently associated with gray matter heterotopia, absence of the septum pellucidum, ACC, and SOD.^{54,98}

Schizencephalic clefts are described as either open-lipped (walls separated) or closed-lipped (walls apposed) and may present unilaterally or bilaterally. The prognosis is worst for patients with bilateral open-lipped schizencephaly.^{97,98} Patients with a unilateral closed-lipped defect have hemiparesis but mild or no cognitive deficits, whereas those with bilateral clefts present with severe developmental delays, microcephaly, hydrocephalus, and spastic tetraparesis. Eighty percent of patients develop epilepsy, most commonly focal seizures.³⁹ Patients with open-lipped schizencephaly have an earlier onset of seizures than do those with closed-lipped schizencephaly; seizures typically start by the age of 3 years.

Genetic mutations and antenatal insults, such as toxic or infectious exposures or vascular compromise, have been implicated in schizencephaly.⁹⁸ Granata et al reported mutations of the *EMX2* gene on chromosome 10q26.1 in their patients with open-lipped schizencephaly.⁹⁹ *EMX2* is expressed by proliferating neuroblasts in the ventricular zone and is responsible for both patterning of the forebrain structure and neuronal migration. However, since first described, mutations of the *EMX2* gene have not been detected in familial cases, suggesting that multiple chromosomal loci are likely involved in the pathogenesis of schizencephaly.^{100,101}

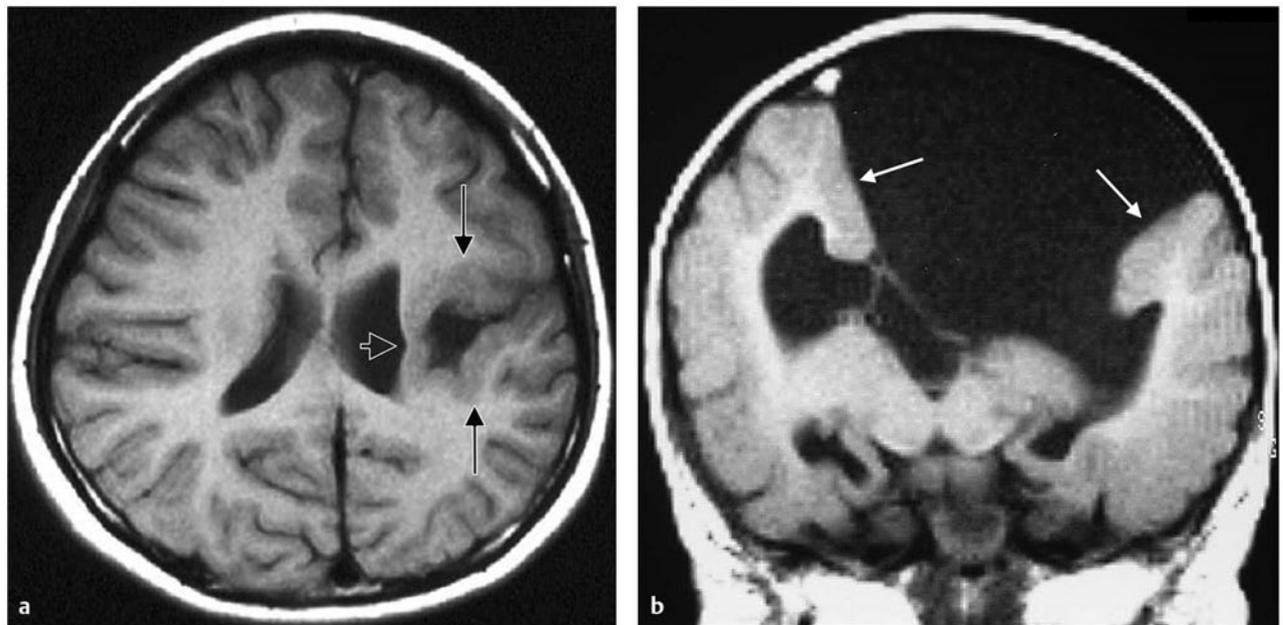


Fig. 15.13 Schizencephaly. (a) Axial T1-weighted magnetic resonance image shows a left unilateral closed-lip schizencephaly. The walls of the transmantle cleft are apposed and lined by gray matter (arrows). Note the deformity in the lateral ventricle, where the ependyma is continuous with the cleft (open arrow). (b) Coronal T1-weighted magnetic resonance image of another child shows gray matter (arrows) lining a left unilateral open-lip cleft.

15.1.17 Porencephaly

Porencephaly, which can be confused with schizencephaly, is lined by gliotic white matter as opposed to dysplastic gray matter. Porencephalic cysts are not malformations. Instead, they are thought to be due to fetal or perinatal intracranial hemorrhage and strokes that result in transmantle destruction of the brain.^{32,102} Maternal and fetal risk factors include cocaine abuse, blood dyscrasias, trauma, and alloimmune thrombocytopenia.

15.1.18 Polymicrogyria

Polymicrogyria is a malformation of cortical development occurring near the end of neuronal migration and during early cortical organization when neurite extension, synaptogenesis, and neuronal maturation normally occur.⁸³ It is categorized as an abnormality of postmigrational development.⁹⁰

Afflicted brain cortices have excessively numerous, small gyri separated by shallow sulci (► Fig. 15.14). The increased number of convolutions results in the appearance of an abnormally thick cortex. Polymicrogyria has traditionally been described as “four-layered” or “unlayered” if there is complete loss of cortical lamination. However, polymicrogyria likely exists as a continuum because the two histologic patterns, and occasionally double- or triple-layered cortices, can occur within the same patient.¹⁰³ These cortical malformations can be focal or widespread and unilateral or bilateral.



Fig. 15.14 Axial T2-weighted magnetic resonance image of polymicrogyria shows an excessive number of small gyri (arrows) at the left temporal lobe and opercular cortex.

Polymicrogyria often coexists with other developmental brain anomalies and is present in most cases of schizencephaly. Most cases of polymicrogyria are sporadic, some of them associated with intrauterine cytomegalovirus infection or compromised placental perfusion.¹⁰⁴ Studies of familial cases indicate that polymicrogyria is genetically heterogeneous and exhibits various patterns of inheritance. Polymicrogyria can be syndromic, especially when it occurs symmetrically in the two hemispheres. In these syndromes, the topology of the affected brain is discrete and consistent, and the clinical symptoms are predictable because they are comparable in similarly affected patients. The most common and best described of these syndromes involves the bilateral perisylvian cortex. Affected individuals have cognitive impairment, epilepsy, and pseudobulbar signs, including dysarthria and dysphagia.^{105,106} Bilateral perisylvian polymicrogyria has an X-linked locus that maps to Xq28, although some patients demonstrate deletions of 22q11.2.

MR imaging of polymicrogyria reveals small irregular gyri, normal or thickened cortices, and an indistinct cortical–white matter junction.¹⁰⁴ In isolated polymicrogyria, the patient’s signs and symptoms correlate with the area of the brain affected. The prognosis varies depending on the extent and location of the malformation, with the sequelae being as minimal as a discrete neurologic impairment or as severe as encephalopathy with intractable seizures.³⁹

15.1.19 Joubert Syndrome

In 1968, Joubert et al were the first to describe a clinical syndrome of alternating hyperpnea and apnea, ataxia, oculomotor apraxia, muscle hypotonia, and intellectual disability in four siblings of consanguineous parents.^{107,108} Subsequent studies of patients with Joubert syndrome describe mid-brain–hindbrain malformation, dysgenesis of the vermis, and fragmentation and hypoplasia of brainstem nuclei and tracts.¹⁰⁹ Affected neonates have a characteristically large head with a prominent forehead, high rounded eyebrows, epicanthal folds, ptosis, a turned-up nose, and a tongue that protrudes irregularly through an open mouth.¹¹⁰ Later in infancy, the children sometimes exhibit behavioral problems, such as separation anxiety, noise hypersensitivity, crying jags, and aggressive behavior.

A deep interpeduncular fossa, elongated and thick superior cerebellar peduncles oriented perpendicularly to the brainstem, and an absent or hypoplastic vermis together give the appearance of a molar tooth on axial-view MR imaging¹¹⁰ (► Fig. 15.15). The MR image may also reveal a cleft vermis with a small dysplastic anterior lobe and an absent posterior lobe. Although the molar tooth sign is most often seen with Joubert syndrome, it is present in other related syndromes, including Dekaban-Arima syndrome, Senior-Löken syndrome, COACH (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, hepatic fibrosis), Váradi-Papp syndrome, Malta syndrome, Joubert plus retinal dystrophy, and Joubert plus

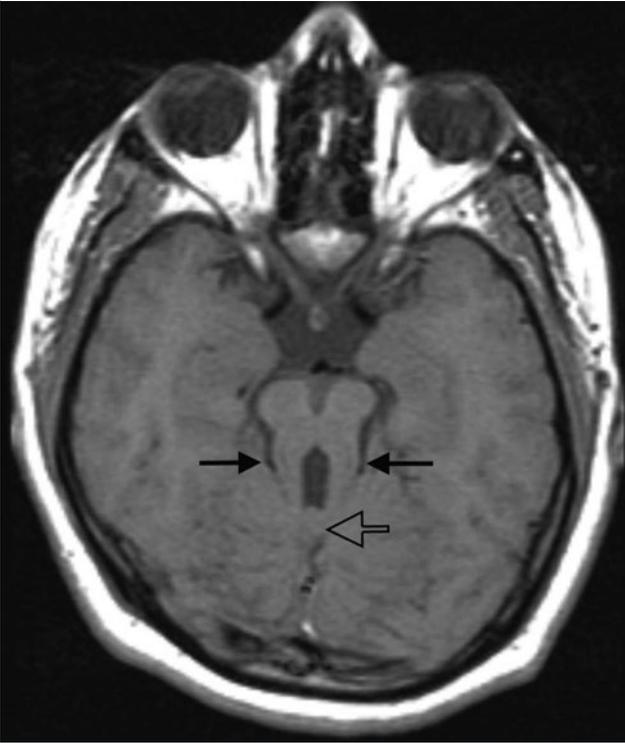


Fig. 15.15 Axial T1-weighted magnetic resonance image through the midbrain of a patient with Joubert syndrome. The deep interpeduncular fossa, thick superior cerebellar peduncles (*arrows*), and hypoplastic vermis (*open arrow*) together give the appearance of a molar tooth.

polymicrogyria.^{111,112} Patients with the related syndromes manifest the classic clinical signs of Joubert syndrome plus various combinations of other distinct features: polymicrogyria, encephalocele, coloboma, hepatic fibrosis, nephronophthisis, polydactyly, renal cysts, retinal dystrophy, and tongue tumors. There is wide phenotypic variability, even among family members, and thus the splitting of Joubert syndrome into other disorders is controversial.

The malformation of the midbrain, upper hindbrain, and cerebellum is thought to evolve from improper patterning of the mesencephalon and metencephalon by the isthmus organizer located at the midbrain–hindbrain boundary.^{109,113} The replacement of genes involved in the development of the isthmus organizer and midbrain–hindbrain patterning in knockout mice causes them to develop malformations similar to those of Joubert syndrome.¹¹⁴ More recent work highlights the role of ciliary defects in the pathogenesis of Joubert syndrome and other ciliopathies such as congenital cerebellar ataxia.¹¹⁵ However, the underlying gene defects resulting in Joubert syndrome are likely heterogeneous. Inheritance is assumed to be autosomal-recessive because of the lack of vertical transmission and increased incidence in children of consanguineous parents.^{110,116}

The prognosis for patients with Joubert syndrome and related disorders is poor. Although some reach the fourth decade of life, the 5-year survival is 50%.^{110,112,116} Survivors suffer cognitive, motor, and visual deficits, as well as other multisystem disorders.¹¹⁰ Survival after infancy dependent upon renal and



Fig. 15.16 Axial T2-weighted magnetic resonance image of rhombencephalosynapsis with a single-lobed cerebellum. There is agenesis of the vermis, and the cerebellar folia fuse across the midline.

hepatic complications, and therefore regular examination by a physician is indicated.

15.1.20 Rhombencephalosynapsis

Rhombencephalosynapsis is a rare malformation first described by Obersteiner in 1916 in a case report entitled *Ein Kleinhirn ohne Wurm*, which is translated as “A Cerebellum without Vermis.” The report detailed the postmortem evaluation of a 31-year-old man.¹¹⁷ This condition is characterized by dorsal fusion of the cerebellar hemispheres with agenesis or severe hypogenesis of the vermis, transversely oriented cerebellar folia, and variable degrees of fusion of the dentate nuclei and middle cerebellar peduncles¹¹⁸ (► Fig. 15.16). The superior cerebellar peduncles, tectum, thalami, and fornices may also be fused. Associated anomalies include hydrocephalus, absent septum pellucidum, fusion of the fornices, HPE, hypoplastic anterior commissure, hypoplastic temporal lobes, gray matter heterotopias, and missing olivary nuclei.^{119–123} Rhombencephalosynapsis can occur in conjunction with two other syndromes, Gómez-López-Hernández syndrome and VACTERL (vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, limb defects).¹²⁴

The pathogenesis is uncertain, but rhombencephalosynapsis may result from improper development of the rhombencephalon at approximately 28 to 45 days of gestation, either from insufficient dorsal induction, defective rhombic lips, or failure of vermian differentiation.^{121,123} More recent studies suggest a

genetic origin, with recurrent cases, parental consanguinity, and diverse chromosomal abnormalities.¹²⁴ The prognosis is highly variable but may be related to the presence of supratentorial anomalies. In cases of isolated rhombencephalosynapsis, patients can have normal cognitive and language function, as did the patient originally described by Obersteiner.^{122,123} Alternatively, patients can have intellectual disability, ataxia, epilepsy, diplegia, and spasticity. Behavioral changes, such as self-mutilation, obsessive-compulsive disorder, and stereotyped “head-rolling” movements, have been reported.¹²⁵ Surgery is needed only for symptomatic hydrocephalus.

15.1.21 Lhermitte-Duclos Disease

Lhermitte-Duclos disease (LDD), also known as dysplastic cerebellar gangliocytoma, is a rare disorder of the cerebellar cortex first described by Lhermitte and Duclos in 1920.¹²⁶ In the more than 150 cases reported since that time, the numbers of males and females are equal. Patients range in age from neonates to the elderly, but many are diagnosed in their third or fourth decade of life.^{127,128} Patients typically present with symptoms consistent with a slowly growing posterior fossa mass. The most frequent complaints associated with LDD are headaches, nausea and vomiting, vertigo, ataxia, gait disturbances, and cranial nerve dysfunction. Additionally, hydrocephalus from compression of the fourth ventricle can cause papilledema, loss of vision, rapid neurologic deterioration, and death.¹²⁷

CT often reveals a fourth ventricle distorted by an iso- or hypodense cerebellar lesion that occasionally contains small areas of calcification. MR imaging of patients with LDD shows a hypointense lesion on T1-weighted images and a characteristic lamination, or “tiger stripe” pattern, composed of thickened cortical folia on T2-weighted images¹²⁷ (► Fig. 15.17). The lesion itself does not enhance after contrast administration; however, proliferating veins within the lesion, as well as the surrounding leptomeninges, can enhance.¹²⁹ The disease usually involves one hemisphere, but it occasionally extends to the vermis or to the contralateral hemisphere.

In LDD, the cerebellar cortex is expanded, and there is a gross reduction of the central white matter. The pale and thickened folia contain hypertrophic granular cells in the internal granular layer that project enlarged and irregularly myelinated axons into the molecular layer.¹³⁰ The Purkinje layer is absent and replaced by granular cells. The presence of ectopic granule neurons in the molecular layer indicates that LDD, in addition to being a disorder of cellular growth, may result from the abnormal inward migration of granule cells from the external granule layer. Some authors have suggested that these cerebellar tumors are neoplastic because of the resemblance of the large granular cells to blastomas, as well as their natural history of growth and possible recurrence after resection.¹³¹ On the other hand, the similar orientation of the enlarged cells to that of normal granule cells, lack of mitotic figures, and low proliferation index underscore their benign character. Recurrence may represent progressive growth of minimally affected regions that appeared normal on MR imaging at the time of initial resection.

The deviant migration and cellular growth in LDD have been linked to germline mutations of the tumor-suppressing phosphatase and tensin (*PTEN*) homologue gene that regulates cell



Fig. 15.17 Axial T2-weighted magnetic resonance image of the posterior fossa of a patient with Lhermitte-Duclos disease shows a hyperintense left cerebellar lesion, with widened folia in a striated pattern, mildly compressing the fourth ventricle.

apoptosis, growth, migration, and differentiation. *PTEN* inactivation results in loss of inhibition of phosphatidylinositol-3-kinase, leading to increased levels of phosphorylated AKT (p-AKT). In turn, p-AKT promotes hypertrophy and survival of the granule cells in LDD via the rapamycin (mTOR) downstream effector.¹²⁸ LDD has been associated with Cowden disease, an autosomal-dominant disorder that also carries germline mutations of *PTEN*.^{127,130} Patients with Cowden disease have mucocutaneous lesions, macrocephaly, systemic hamartomas (including LDD), and neoplasms of the breast, thyroid, genitourinary tract, and endometrium. However, a minority of patients with LDD do not have manifestations of Cowden disease. These are typically children at the time of diagnosis and lack the *PTEN* mutation, despite activation of mTOR.^{128,132}

Although LDD is benign, the definitive treatment is prompt surgical resection because of the mass's propensity to grow. The lack of a sharp border between the tumor and normal cerebellar tissue accounts for a recurrence rate that approaches 30%.¹²⁸ Patients require genetic testing and a thorough search for concomitant neoplastic or hamartomatous lesions associated with Cowden disease. Patients with a diagnosis of LDD require long-term follow-up because of the high risk for recurrence, probable inheritance, and need for the early detection of potential cancers.

15.1.22 Cerebellar Hypoplasia

Hypoplasia of the cerebellum can be isolated to the vermis or diffusely involve the vermis and hemispheres, and it includes the Dandy-Walker malformation. Both forms are heterogeneous conditions and are a feature in a variety of intracranial and extracranial malformation syndromes. Patients with Dandy-Walker malformation characteristically have cystic dilatation of the fourth ventricle and enlargement of the posterior fossa with upward displacement of the tentorium and torcular, in addition to partial or complete agenesis of the vermis. Diffuse cerebellar hypoplasia is associated with ciliopathy; trisomies 13, 18, and 21; granule cell hypoplasia; cerebral and cerebellar migration disorders; and intrauterine exposure to teratogens.^{133,134} Because the cerebellum is also involved with cognitive functions, affected infants develop learning disabilities, as well as motor deficits. In Dandy-Walker malformation, the psychomotor impairment is often potentiated by supratentorial anomalies, including hydrocephalus, which is seen in up to 90% of children, dysgenesis of the corpus callosum, and HPE.^{135,136} Patients with unilateral hemispheric hypoplasia have mild or no symptoms, and it is assumed to be a consequence of a vascular insult, not a malformation.¹²³

Isolated cerebellar vermis hypoplasia also has a favorable prognosis. However, when vermian hypoplasia coexists with cerebral cortical malformations, it either is inherited as an X-linked disorder or is part of a syndrome, and it is associated with severe intellectual disability.^{133,134} On imaging, patients have a hypoplastic but normally positioned vermis and an enlarged fourth ventricle that communicates with a small, retrocerebellar cerebrospinal fluid space. Although cerebellar vermis hypoplasia appears similar to and is often diagnosed as a Dandy-Walker variant, it is thought to be unrelated etiologically to Dandy-Walker malformation.¹³⁶

15.1.23 Pontocerebellar Hypoplasia

Hypoplasia of the cerebellum is common to a variety of disorders. Concomitant mild hypoplasia of the pons will result if there is loss or atrophy of the large transverse fibers between it and the cerebellum. The distinguishing feature of pontocerebellar hypoplasia (PCH), which occurs rarely, is the paucity of pontine neurons. PCH is a devastating condition characterized by multiple structural abnormalities of the pons, dentate, inferior olive, and cerebellum. Disruption of the rhombic lip during cerebellar development is the suspected pathogenesis because the rhombic lip is the source of neuron precursors for the cerebellum and the pons. PCH classifications have evolved over the last 10 years to include seven types at present,¹³⁷ but types 1, 2, and 4 (also known as olivopontocerebellar atrophy, or OPCA) are most frequently described. PCH is an autosomal-recessive disorder with several genes implicated in its pathogenesis, including *TSEN54*, *RARS2*, *CLAM*, and *VRK1*.^{133,134,137}

An infant with PCH type 1 has characteristic degeneration of the spinal anterior horn cells, resembling infantile spinal muscular atrophy, as well as degeneration of the dentate nuclei and neurons of the pons. The defects result in respiratory and swallowing difficulties, central or peripheral motor dysfunction with hypertonia or hypotonia, and muscle contractures. These children often require mechanical ventilation at

birth and all die by the age of 1 year, often of respiratory complications. The hallmark of PCH type 2 is continuous extrapyramidal dyskinesia during waking, which starts as chorea and then evolves to dystonia later in childhood. The child does not exhibit any cognitive or motor development but has an early onset of seizures. Microcephaly results from progressive atrophy of the cerebrum. The dominant symptoms of PCH type 4 are cerebellar, including disequilibrium, ataxia, and dysarthria, and do not clinically manifest until youth or the middle years.¹³⁸ MR images of the brain in patients with PCH types 1, 2, and 4 are similar: cerebellar hemispheres that are reduced to winglike structures positioned just below the tentorium, a hypoplastic vermis with all lobes preserved, and absence of a pontine bulge (► Fig. 15.18).

15.2 Fetal Imaging

Early in utero diagnosis of congenital anomalies guides the parents' decision concerning the continuation of pregnancy and the physicians' plans for possible fetal surgery, mode of delivery, and postpartum care. Fetal ultrasonography is the standard modality for screening and evaluation of the CNS, although because of its increasing availability, fetal MR imaging may soon supplant sonography as the standard. Ultrasonography remains widely available and is cost-effective. However, its accuracy depends on the experience of the ultrasonographer and is potentially limited by maternal obesity, oligohydramnios, and adjacent bony structures.¹³⁹ The



Fig. 15.18 Midsagittal T1-weighted magnetic resonance imaging of pontocerebellar hypoplasia. The vermis and cerebellar hemispheres are hypoplastic, and the ventral pons is flat.

limited view of standard ultrasound images can be overcome with three-dimensional sonography. Nevertheless, MR imaging adds a level of diagnostic accuracy notably better than that of ultrasonography¹⁴⁰

Fetal ultrasound can easily detect large anatomical defects specific to a malformation that otherwise would not be diagnosed until after birth. However, knowledge of the CNS embryology and its appearance on ultrasound at different gestational stages is important in avoiding incorrect diagnoses. For example, dysgenesis of the corpus callosum cannot be diagnosed until the 20th gestational week, when development of the commissure is normally complete. The cerebellar hemispheres and vermis continue to develop until after birth and can appear similar to cerebellar hypoplasia until the sixth or seventh month of gestation, when the posterior fossa cerebrospinal fluid space is replaced by brain.¹³⁹ On the other hand, obliteration of the cisterna magna, along with the lemon sign, banana sign, and possibly hydrocephalus, is consistent with Chiari malformation.¹⁴¹ Mildly enlarged ventricles are often normal in young fetuses, but the risk for developing hydrocephalus and having associated anomalies is significant when the ventricular width is greater than 15 mm.¹⁴² Extracerebral findings, such as facial dysmorphism and polyhydramnios, can also be indicators of CNS anomalies.¹⁴³

Subtle abnormalities, such as a smooth cortex in lissencephaly, can be difficult to detect by transabdominal ultrasound, even after 28 weeks of gestation, when the sulci and gyri are well defined. Difficult cases may be clarified by transvaginal neurosonography of the head in cephalic presentation, but these are ideally investigated with MR imaging of the fetus. Fast acquisition of images with the single-shot fast spin echo and half-Fourier acquisition single-shot turbo spin echo (HASTE) techniques minimizes artifacts caused by fetal movement.¹³⁹ It surpasses ultrasound in its anatomical resolution, size of the field of view, and ability to be reconstructed in multiple planes. The accuracy of MR imaging depends on the fetus's gestational age and is ideally delayed until the 20th week. More recent MR techniques add to the increasing armamentarium available for clinical diagnosis.¹⁴⁴

15.3 Surgical Treatment

The surgical treatment of congenital brain malformations is currently limited to the excision of mass lesions (LDD and congenital neoplasms) and dermal sinuses, repair of encephaloceles, shunting of cerebrospinal fluid for hydrocephalus, and epilepsy surgery. Of these, chronic epilepsy is the most difficult to manage, medically as well as surgically. The malformations associated with seizures are diverse, and the seizure semiology of each lesion type is mixed. In the largest study evaluating pediatric epilepsy with brain malformations, dysgenesis of the corpus callosum was the most frequent MR imaging finding, followed by equal numbers of cases of lissencephaly and focal cortical dysplasia, and finally pachygyria.¹⁴⁵ However, 80% of patients with dysgenesis of the corpus callosum and 55% of patients with lissencephaly had other brain anomalies. Other primary findings on MR imaging in epileptic children were polymicrogyria, heterotopia, schizencephaly, HPE, and hemimegalencephaly. In the study, the

seizures usually began early during infancy and often responded poorly to anticonvulsants.^{145,146}

Surgery for seizures is considered when all medical treatment options are exhausted. Preoperative MR imaging can reveal areas of abnormal gyri, thickened cortex, poor gray-white differentiation, and hyperintensity on T2-weighted images. Unfortunately, ideal candidates who have a surgically amenable unilateral lesion that correlates with preoperative fluorodeoxyglucose F 18 positron emission tomography (FDG-PET) and electroencephalography findings are infrequent. Seizure-free outcome after surgery for malformations of cortical development can be achieved in up to 50% of cases, but this success rate is low in comparison with those of surgery for hippocampal sclerosis.^{147,148} The lower success rate may be due to the coexistence of subtle dysplasias not detected by MR imaging and the presence of multiple epileptogenic zones that can be distant from, or even on the side opposite to, the visualized abnormality.¹⁴⁹ Patients with bilateral malformations and hemimegalencephaly have the least favorable outcomes, even after hemispherectomy for the latter.^{147,150,151}

Pearls

In these authors' experience:

- Most hemispheric malformations can be detected by fetal ultrasound, but subtle anomalies, especially those of the posterior fossa, require evaluation by in utero or postnatal MR imaging.
- In holoprosencephaly, the severity of facial dysmorphism may correlate with the degree of hemispheric noncleavage.
- Developmental delay is a common clinical presentation of hemispheric malformations but is also seen with cerebellar malformations.
- Seizures are usually associated with disorders of neuronal proliferation, differentiation, and migration and cortical organization. They often present early in life and become resistant to anticonvulsants.
- The child's neurologic prognosis depends upon the severity of the malformation and seizures.
- The surgeon's role in helping children with brain malformations attain their developmental potential is providing prompt surgery for hydrocephalus, tumors, and debilitating seizures.

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16 Chiari Malformations

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16.1 History and Classification

In the early 1890s, Dr. Hans Chiari¹ used autopsy specimens to describe four congenital anomalies, later termed the Chiari malformations (► Table 16.1). The four traditional varieties of Chiari malformation represent varying degrees of involvement of rhombencephalic derivatives. Three of these (types 1 through 3) have progressively more severe herniation of these structures outside the posterior fossa as their common feature. These three types also have in common a pathogenesis that involves a loss of the free movement of cerebrospinal fluid (CSF) out of the normal outlet channels of the fourth ventricle. Pathologic differences between Chiari 1 malformations (C1Ms) and Chiari 2 malformations (C2Ms) can be explained with knowledge of the differences in the timing of the development of the vector of force across the foramen magnum.

Although a large majority of cases are congenital, acquired C1Ms occur and are not rare. Not considered further in this chapter are the patients who have movement of their cerebellar tonsils into the cervical spine because of an intracranial tumor or other mass, especially within the posterior fossa. Technically, these patients have a C1 M, but treatment of the cause of their hindbrain hernia usually allows resolution of their secondary C1 M.

Several subclassifications have been developed for patients with hindbrain hernias, which are due to some problem with equilibrating CSF across the craniocervical junction. These classifications are as follows.

16.1.1 Chiari 0

Patients who do not appear to have significant hindbrain hernias, even though the posterior fossa may appear “crowded,” and who have large syringes that resolve with posterior fossa

decompression are classified as having Chiari 0 malformation.² Their condition indicates that they have a fourth ventricular outlet obstruction, and at surgery they frequently do have physical barriers to CSF movement but do not have caudal displacement of the cerebellar tonsils beyond a point that could be considered pathologic (<5 mm). These patients are included in the current chapter because their presentation and surgical intervention are the same as those of patients with frank hindbrain herniation.

16.1.2 Chiari 1

Patients in this common group have caudal displacement of the cerebellar tonsils more than 5 mm below the foramen magnum (► Fig. 16.1). The brainstem is in a normal position. They may or may not have a syrinx. The 5-mm “rule” concerning the definition of the pathologic extent of the caudal migration of the tonsils is arbitrary. Numerous patients have tonsils well below this point and are asymptomatic, especially young infants and children. When followed over time, they frequently remain asymptomatic if their initial evaluation was performed for an unrelated reason. The extent of their caudal migration may progressively decrease with time and become less impressive. This, however, is not certain, and the patient should be followed for the development of symptoms. A host of conditions are associated with the C1M. Many are listed in the box “Reported Associations with Chiari 1 Malformations (p. 193).”

Table 16.1 The classic Chiari malformations

Type	Characterized by:
Chiari type 1	Tonsillar herniation > 5 mm inferior to the McRae line No associated brainstem herniation or supratentorial anomalies Hydrocephalus uncommon Syringomyelia common
Chiari type 2	Herniation of the cerebellar vermis, brainstem, and fourth ventricle through the foramen magnum Almost always associated with myelomeningocele and multiple brain anomalies(see box “Findings Associated with Chiari 2 Malformations”)Hydrocephalus and syringomyelia very common
Chiari type 3	Foramen magnum encephalocele containing herniated cerebellar and brain stem tissue
Chiari type 4	Hypoplasia or aplasia of the cerebellum and tentorium cerebelli

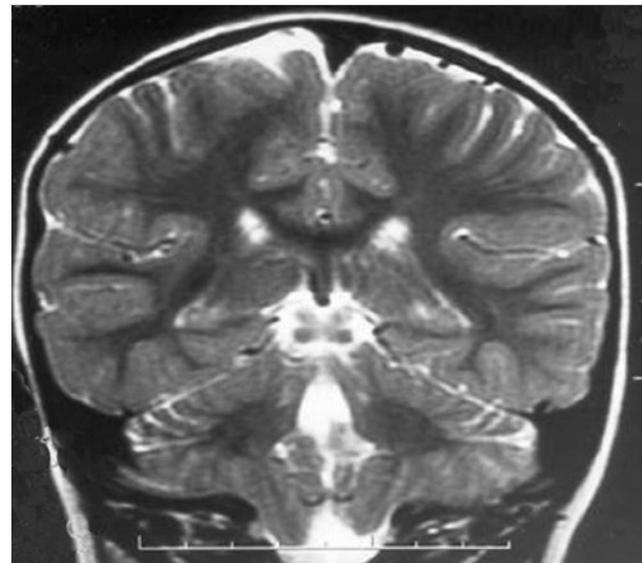


Fig. 16.1 Coronal magnetic resonance image demonstrating a Chiari 1 malformation. Note the asymmetry of the descended cerebellar tonsils.



Fig. 16.2 Sagittal magnetic resonance image illustrating tonsillar ectopia and caudal descent of the brainstem (i.e., the Chiari 1.5 malformation). Note the extensive syringomyelia with a skip region at C1–C2.

Reported Associations with Chiari 1 Malformations

- Klippel-Feil anomaly
- Odontoid retroflexion
- Growth hormone deficiency
- Neurofibromatosis
- Pierre Robin syndrome
- Costello syndrome
- Caudal regression syndrome
- Hemihypertrophy
- Lipomyelomeningocele
- Crouzon syndrome
- Apert syndrome
- Multisutural craniosynostosis
- Paget disease
- Craniometaphyseal dysplasia
- Rickets
- Acromegaly

16.1.3 Chiari 1.5

Although somewhat confusing, this term is applied to patients who bridge the gap between C1 M and C2 M. They have characteristics of both groups and are best considered separately. Their malformations are unassociated with neural tube defects, and caudal displacement of the cerebellar tonsils is similar to that in patients with C1 M. However, their brainstem and fourth ventricle are low, like those in patients with C2 M (► Fig. 16.2). In our series of patients without a neural tube defect and a hindbrain hernia, 17% had significant caudal displacement of the brainstem.³ Based on our series, these patients appear to have a greater chance of developing syringomyelia.

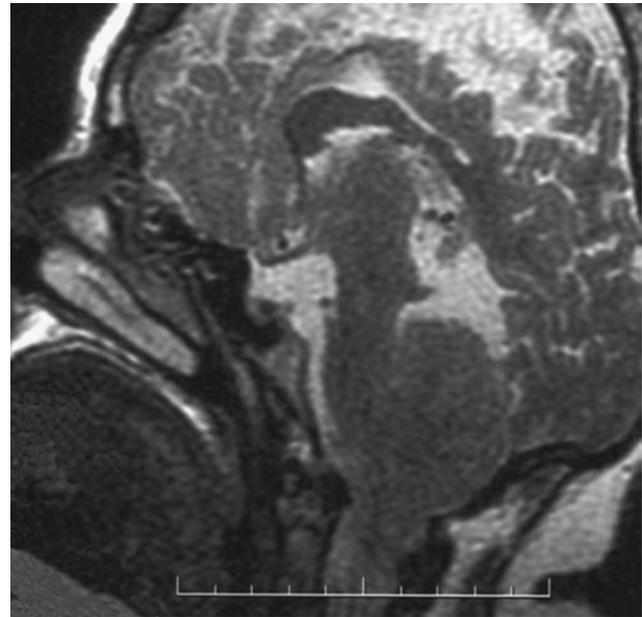


Fig. 16.3 Vermian herniation in the Chiari 2 malformation as demonstrated on a sagittal magnetic resonance image.

16.1.4 Chiari 2

This lesion occurs in patients with neural tube defects (myelomeningoceles and encephaloceles). It consists of caudal migration of the cerebellar vermis rather than of the cerebellar tonsils, brainstem, and fourth ventricle (► Fig. 16.3). Syringomyelia is common, as are a host of additional findings (see box “Findings Associated with Chiari 2 Malformations (p.193)”).

Findings Associated with Chiari 2 Malformations

- Skull
 - Craniolacunias
 - Scalloping of the petrous bones
 - Foreshortening of the internal acoustic meatus
 - Enlarged foramen magnum
 - Small posterior fossa
 - Notching of the opisthion
 - Scalloping of the frontal bone (lemon sign)
 - Cranioschisis
 - Clival concavity
 - Inferiorly displaced inion
 - Midline occipital keel
 - Assimilation of the atlas
- Spine
 - Enlarged cervical canal
 - Scalloping of the odontoid process
 - Incomplete posterior arch of C1
 - Klippel-Feil deformity
 - Basilar invagination

- Ventricle/cistern
 - Hydrocephalus
 - Asymmetry of the lateral ventricles
 - Lateral pointing of the frontal horns
 - Colpocephaly
 - Shark tooth deformity of the third ventricle
 - Commissure of Meynert
 - Small fourth ventricle that is flat and elongated
 - Extraventricular location of the choroid plexus of the fourth ventricle
 - Absence of the inferior medullary velum
 - Absence or cyst of the foramen of Magendie
 - Enlarged cerebellar and pontine cisterns
- Meninges
 - Widened, heart-shaped, low-lying, hypoplastic, venous lake-engorged tentorium cerebelli
 - Vertical straight sinus
 - Confluence of sinuses near opisthion
 - Falx cerebri/cerebelli hypoplasia/aplasia
 - Thickening of the leptomeninges at the foramen magnum
 - Arachnoid cysts of the cervical canal
 - Thickening of the cephalic dentate ligaments
- Spinal cord
 - Split-cord malformation
 - Syringomyelia
 - Exophytic syringes
 - Shortened and caudally displaced cervical spinal cord
 - Reduced neuronal counts in the cervical cord
 - Reduction in myelination of the corticospinal tracts
- Telencephalon
 - Complete or partial agenesis of the corpus callosum and/or septum pellucidum
 - Polygyria
 - Chinese lettering (interdigitation of the parieto-occipital lobes)
 - Agenesis of the olfactory tract and bulb
 - Agenesis of the cingulate gyrus
 - Prominence of the head of the caudate nucleus
 - Heterotopias
- Diencephalon
 - Enlarged massa intermedia
 - Anterior displacement of the massa intermedia
 - Elevation of the hypothalamus
 - Elongation of the habenular commissure and pineal gland
- Mesencephalon
 - Elongation of the midbrain with a shortened tectum
 - Tectal beaking (fusion of the superior and inferior colliculi)
 - Stenotic, stretched, forked, or kinked cerebral aqueduct
- Metencephalon
 - Small cerebellum that may tower superior to the tentorium cerebelli
 - Vermian herniation through the foramen magnum
 - Cranial nerves that traverse the cerebellar folia and that may be dysplastic
 - Curvature (inversion) of the cerebellum with resultant “kissing” of the left and right sides (banana sign) anterior to the brainstem
 - Cerebellar heterotopias
 - Dysplastic deep gray matter

- Elongation of the pons with indentation of its ventral surface
- Caudal displacement of the basivertebral arteries
- Dysplastic pontine basal nuclei
- Dysplastic tegmental and cranial nerve nuclei of the pons
- Myelencephalon
 - Elongation and flattening of the medulla producing a “trumpet-like” structure
 - Protuberance (medullary kink, hump, spur, buckle) caudal to the gracile and cuneate tubercles
 - Cephalically located pyramidal decussation

16.1.5 Chiari 3

The Chiari 3 malformation is a rare and extreme form of hindbrain hernia. It is found in fewer than 1% of all patients in this category. Patients have a high cervical sac containing significant portions of the cerebellum and/or brainstem. There are frequently other associated anomalies, similar to those in patients with C2 M (► Fig. 16.4). Hydrocephalus is common, and severe neurologic and developmental problems are usually present. Treatment consists of ensuring that skin covers the lesions and that tethering is not an issue. This malformation will not be considered further because of its rarity and the limited role that neurosurgery plays in its care.

16.1.6 Chiari 4

Patients with type 4 Chiari malformation have cerebellar hypoplasia or aplasia. This is not a form of hindbrain hernia. Therefore, inclusion in a discussion of hindbrain hernias is questionable, and this malformation will not be considered further.

16.2 Signs and Symptoms

16.2.1 Chiari 1 Malformations

Patients with a C1 M may present with a variety of symptoms and signs ranging from headache to severe myelopathy and brainstem compromise (see box “Clinical Presentation of a Chiari 1 Malformation (p.195)”). The most common presenting symptom is pain (60 to 70%),⁴ usually occipital or upper cervical in location and often induced or exacerbated by Valsalva maneuvers such as coughing, laughing, and sneezing. In infants and children who are unable to communicate verbally, headaches may be manifested simply by irritability or grabbing at the neck.⁵ As many as half of the patients with a Valsalva-induced headache will be found to have a C1 M as the cause. If the headache is not Valsalva-induced and if the pain is farther away from the craniocervical junction, it is less likely that a hindbrain hernia is the cause. Adolescents who have a symptom complex with vague frontal or vertex headaches, no syrinx, a normal neurologic examination, and a descent of the tonsils of 5 mm or more is very unlikely to improve symptomatically if a Chiari decompression is performed. This should be contrasted with the 6-month-old child who cries and then reaches for the posterior cervical region, grimaces, and arches the spine. In this case, the original neck pain is relieved postoperatively.

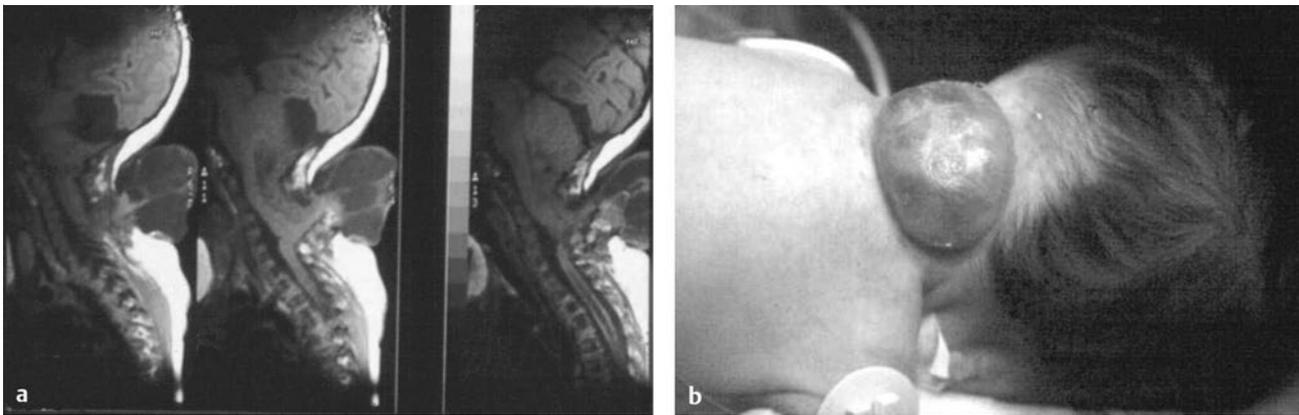


Fig. 16.4 (a) Sagittal magnetic resonance images and clinical image of a type 3 Chiari malformation, (b) with hindbrain herniation through an upper cervical spina bifida.

Clinical Presentation of a Chiari 1 Malformation

- Symptoms
 - Occipitocervical headaches/dysesthesia
 - Nonradicular pain in the back, shoulders, and limbs
 - Motor and sensory symptoms
 - Clumsiness
 - Dysphagia
 - Dysarthria
- Cerebellar syndrome
 - Truncal and appendicular ataxia
- Brainstem syndrome
 - Respiratory irregularities
 - Nystagmus
 - Lower cranial nerve dysfunction, including otologic disturbances
 - Recurrent aspiration
 - Hypertension (rare)
 - Glossal atrophy
 - Facial sensory loss
 - Trigeminal or glossopharyngeal neuralgia
- Spinal cord syndrome
 - Motor and sensory losses, especially in the hands
 - Hyporeflexia
 - Hyperreflexia
 - Babinski response
- Other signs
 - Oscillopsia
 - Esotropia
 - Sinus bradycardia
 - Progressive scoliosis
 - Hoarseness
 - Hiccups
 - Urinary incontinence
 - Drop attacks
 - Scoliosis

Another major symptom complex includes scoliosis. Scoliosis associated with syringomyelia may sometimes be differentiated from idiopathic scoliosis by a left thoracic curve, abnormal abdominal reflexes, or diffuse nondermatomal pain in the flank or back. Any neurologic abnormality, uncharacteristic pain, or other worrisome change in a patient with scoliosis should alert the clinician to the possibility of a syrinx caused by a C1 M.

Other unique symptom complexes may be grouped according to the anatomical area affected: brainstem and cranial nerves, spinal cord, and cerebellum.

Symptom complexes that localize to the brainstem include tongue atrophy, downbeat nystagmus (indicative of medullary dysfunction), and extraocular muscle changes (even an isolated sixth nerve palsy or paresis). Lower cranial nerve dysfunction may occur in 15 to 25% of patients, with gagging, sleep apnea, and difficulty swallowing.⁶⁻⁸ Oropharyngeal dysfunction is common and can manifest as poor feeding, failure to thrive, recurrent aspiration pneumonia, and dysphagia.⁹ Vocal cord paralysis with stridor or hoarseness is rarely present and is similar to the symptoms of patients with C2 M.

Spinal cord dysfunction is the result of direct cord compression or a syrinx (► Fig. 16.5, ► Fig. 16.6, and ► Fig. 16.7). Older adolescents may describe the classic suspended, dissociated sensory loss, but this will rarely be a spontaneous complaint. The loss of pain and temperature sensation with preservation of light touch and proprioception, when present, will appear over the trunk or hands. This occurs as the crossing fibers are damaged by the progressive enlargement of the intramedullary process. The mechanism of causation of scoliosis is not fully understood. It can be argued that the asymmetric weakness of the paravertebral musculature causes a postural imbalance that manifests as scoliosis.

Interestingly, cerebellar dysfunction as a presentation is rare. Cerebellar signs, other than nystagmus, are also rare. There is no apparent neurologic localization for the cerebellar tonsils, despite the presence of gliosis and ischemia commonly seen at operation.

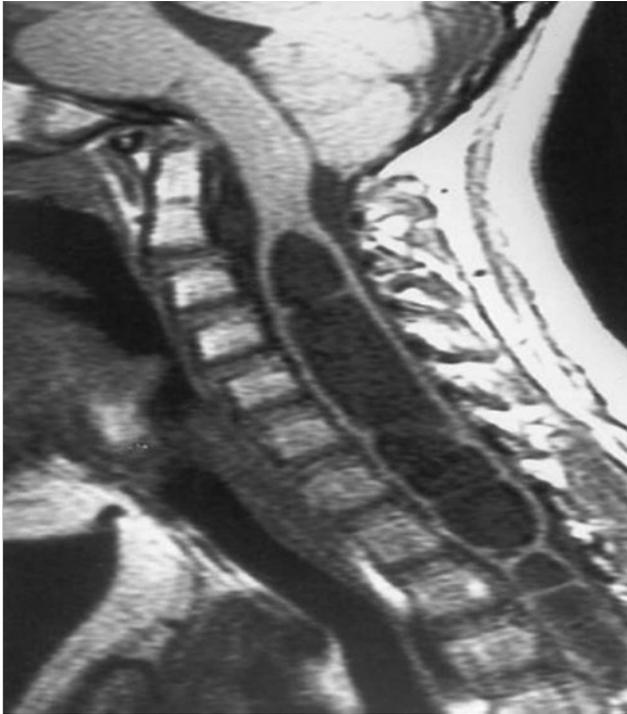


Fig. 16.5 Sagittal magnetic resonance image of a patient with Chiari 1 malformation and a huge syringomyelia. Note the septa (haustri) within the syrinx.



Fig. 16.6 T2-weighted sagittal magnetic resonance image of a patient with Chiari 1 malformation. Note the tonsillar level of C2 and the small cervical syrinx.

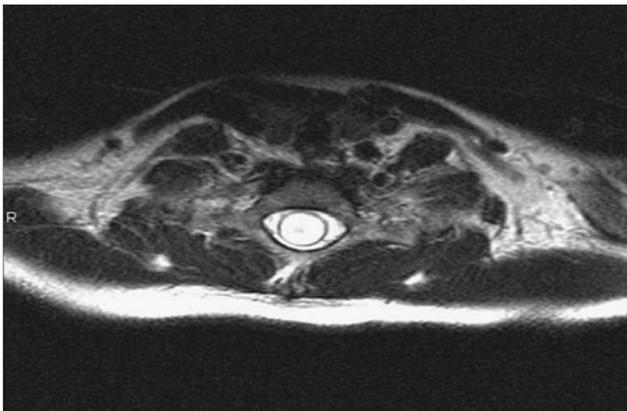


Fig. 16.7 Axial magnetic resonance image through the cervical portion of a holocord syrinx in a young girl. Note the extremely thin nature of the spinal cord. This patient surprisingly had very little symptomatology and presented with scoliosis.

16.2.2 Chiari 2 Malformations

Symptoms of C2M occur characteristically within age groups. As many as one-third of neonates and infants with myelomeningocele may present with serious life-threatening apnea,

inspiratory stridor, dysphagia, and bradycardia. The apnea is frequently associated with breath-holding spells. The dysphagia may be so severe that there is a failure to thrive. When these symptoms are present at birth, the situation is grave and implies hypoplasia or aplasia of the appropriate medullary nuclei. If present at birth, the symptoms are generally not reversible. It is more common that medullary symptoms begin within the first few months of life. They may be associated with opisthotonos. When these symptoms develop, normalization of the intracranial pressure with shunt insertion or revision is necessary for active support of the infant.

With regard to the inspiratory wheezing so characteristic of this situation, the “crowing” sound tends to fluctuate with time, increasing with anxiety and diminishing with sleep. When the sound is present while the patient is at rest, the situation is critical and warrants urgent attention.

Older children most commonly display symptoms and signs of spinal cord compromise, with lower motor neuron problems in the arms and upper motor signs and symptoms in the legs. Hyperreflexia in the legs of a patient with myelomeningocele generally requires investigation.

As in patients with C1 M, cerebellar signs (other than nystagmus) are uncommon and very rarely a reason for clinical presentation. The box “Clinical Presentation of the Chiari 2 Malformation (p. 197)” summarizes the clinical presentation of patients with C2 M.

Clinical Presentation of the Chiari 2 Malformation

- Newborns
 - Usually asymptomatic
- Infants
 - Signs of brainstem compression
 - Stridor secondary to vocal cord paralysis
 - Central and obstructive apnea
 - Aspiration secondary to dysphagia with potential pneumonia
 - Failure to thrive secondary to dysphagia
 - Breath-holding spells with possible loss of consciousness
 - Hypotonia and quadriparesis
 - Irritability
 - Opisthotonos
- Older children and young adults
 - Spinal, cerebellar, and ophthalmologic signs
 - Occipitocervical pain
 - Hand weakness and loss of muscle bulk
 - Myelopathy
 - Ataxia
 - Strabismus
 - Nystagmus
 - Defects of pursuit movements and convergence
 - Defects of optokinetic movements
 - Scoliosis
 - Dysarthria
- Neurologic emergency
 - Usually younger than 2 years, commonly by 3 months of age
 - Progressive neck pain
 - Apnea
 - Dysphagia
 - Stridor
 - Opisthotonos
 - Nystagmus
 - Progressive brainstem dysfunction

16.3 Diagnostic Studies

16.3.1 Computed Tomography and Magnetic Resonance Imaging

Chiari 1 Malformations

C1 M consists of significant herniation of the cerebellar tonsils through the foramen magnum. Reasonable criteria for this diagnosis include herniation of one or both tonsils at least 5 mm below the foramen magnum accompanied by other C1 M features, such as syringomyelia.¹⁰ The tonsillar tip may be pointed, carrying further pathologic significance, or be blunt and rounded, causing less concern. The foramen magnum will appear crowded, with a lack of CSF surrounding the tonsils on T2-weighted magnetic resonance (MR) imaging. In addition, accurate diagnostic guidelines should include the absence of an intracranial mass lesion or hydrocephalus. The liberal use of MR imaging over the last 20 years has greatly facilitated the diagnosis of C1 M and increased its apparent incidence. The true incidence of C1 M is not known. However, in 7,400 brain

dissections, Friede¹¹ found 2 cases plus 46 additional examples of “chronic tonsillar herniation,” which may include many patients who are now classified as having a C1 M.

In an early review of 800 MR imaging examinations, one study¹² noted that “normal” or “asymptomatic” patients might have tonsils that extend 3 mm below the foramen magnum. The tonsillar herniation was much more likely to be pathologic when it exceeded 5 mm. Similarly, Barkovich et al¹³ studied 200 normal patients and 25 patients with a “firm” diagnosis of C1 M. A distance of 2 mm below the foramen magnum was considered the lowest extent of the tonsils in normal patients (specificity of 98.5%, including three false-positive results, and sensitivity of 100%). A distance of 3 mm below the foramen magnum was considered the lowest extent in normal patients (sensitivity of 96% and specificity of 99.5%). An additional study has documented ascent of the tonsils with increasing age.¹⁴

From these studies, it is clear that the practicing pediatric neurosurgeon will see frequent exceptions to the measurements listed above. These studies are useful in screening patients, but the symptom complexes must be analyzed together with the radiologic findings. Patients imaged early in life for unrelated reasons and asymptomatic for Chiari symptomatology may have very impressive MR images. Observing numerous patients in this category who are without symptoms or a syrinx has led us to advocate a conservative approach to intervention. However, operative intervention should be considered for patients with a large syrinx and unimpressive hindbrain herniation and no other cause for the syrinx.

Other associated radiologic anomalies occur infrequently; they most commonly include atlanto-occipital assimilation, basilar invagination, and fused cervical vertebrae. These findings are important to know before surgical positioning.

The combination of hydrocephalus and a C1 M is a special subject and is covered later in this chapter. It must be excluded before a family is advised on a course of action.

Chiari 2 Malformations

Patients with a C2 M are characterized by (1) elongation and caudal displacement of the cerebellar vermis and brainstem structures, (2) the presence of a myelomeningocele or encephalocele in virtually all cases, and (3) hydrocephalus in the majority of cases. Syringomyelia is also commonly seen in this situation (40 to 95%), especially in the lower cervical cord. Other anomalies associated with C2 M (see box “Findings Associated with Chiari 2 Malformations (p. 193)”) comprise a set of cranial and spinal malformations. None of these findings is in itself pathognomonic for a hindbrain hernia, but their coexistence is suggestive of a C2 M (► Fig. 16.8 and ► Fig. 16.9). Studies that might be performed in addition to computed tomography (CT) and MR imaging include sleep studies to evaluate for sleep apnea, swallowing studies to demonstrate cricopharyngeal achalasia, and laryngoscopy to verify movement of the vocal cords.

16.3.2 Pathology and Pathobiology

Although the different types of Chiari anomalies involve many of the same anatomical structures, their pathoembryologic origins appear to be distinct. In this section, we attempt a historical overview of the main theories of the first two types of Chiari



Fig. 16.8 Magnetic resonance image of a Chiari 2 malformation. Note the dysplasia of the corpus callosum, large massa intermedia, flattened pons and medulla, vermian herniation and upward herniation of the cerebellum, tectal beaking, and caudal descent of the confluence of the sinuses.

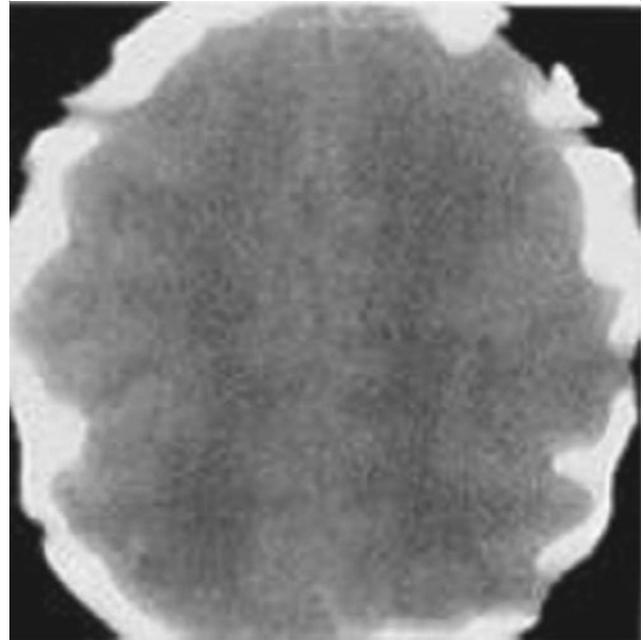


Fig. 16.9 Computed tomographic scan of a Chiari 2 malformation. Note the prominent craniolacunia.

malformations in an effort to understand the anatomy of these lesions and some of the logic behind the different therapeutic strategies. It is important to note that any acceptable theory of the pathogenesis of Chiari malformations should be able to explain the associated brain and spinal cord malformations.

In his initial description, Chiari¹ suggested that hindbrain hernias resulted from hydrocephalus, and that the different Chiari malformations consisted of degrees of expression of that same mechanism. Since then, several other theories have been presented; these distinguished between the embryology of the different malformations and debated whether some of the lesions were purely dysraphic or the result of the interplay of intracranial and intraspinal mechanical forces. Chiari's description of acquired Chiari malformations, together with the demonstration of dynamic shifts on cine-mode MR imaging, suggests that Chiari malformations are not merely fixed dysraphic lesions. Instead, they may be dynamic entities that can change with time.

The theories of the pathogenesis of Chiari malformations include the hindbrain dysgenesis and developmental arrest theory, the caudal traction theory, the hydrocephalic and hydrodynamic theory of Gardner, the small posterior fossa/hindbrain overgrowth theory, and the lack of embryologic ventricular distention theory.¹⁵

Chiari believed that the first three types of malformation resulted directly from chronic hydrocephalus. In his 1891 article,¹ he stated that he had never seen a hindbrain hernia that was not associated with hydrocephalus; he added that chronic hydrocephalus could possibly cause the cerebellum to develop abnormally and to herniate into the foramen magnum. The occurrence of Chiari malformations without hydrocephalus and the coexistence of other anomalies, such as myelomeningoceles and split-cord malformations, was much more involved. In addition, one of the most significant components of C2Ms is the

upward herniation of posterior fossa structures through the tentorial notch into the supratentorial compartment. This too would not be consistent with such a theory.

One of the earliest views of pathogenesis stated that tethering of the spinal cord might cause the posterior fossa structures to be pulled down into the spinal canal. Aside from the fact that this theory could not explain the cervicomedullary kink and other Chiari 2 anomalies, experimental evidence in animals has disproved the theory altogether.

In his original description of a hindbrain hernia in an autopsy specimen with a myelomeningocele, Cleland was the first to support the dysraphic theory.³⁵ Recent pathologic studies have demonstrated aplastic or dysplastic changes in the brainstem specifically affecting the cranial nerve nuclei, cerebellum, thalamus, and corpus callosum, further supporting a dysgenesis theory. Nonetheless, this theory has been found to be inadequate because it still does not explain the other cranial malformations found in these patients and is not compatible with the dynamic shifts outlined above.

In the 1950s and early 1960s, Gardner¹⁶ presented his hydrodynamic theory, which stated that in normal embryology, CSF pulsations from the choroid plexus (previously described by Bering)¹⁷ play a significant role in the expansion of the neural tube).¹⁷ was later significantly expanded by Williams.¹⁸ According to Gardner, these pulsations help in the development of the arachnoid pathways, as well as in the modeling of the expanding brain. He believed that the balance between the pulsatile flow in the supratentorial and fourth ventricular choroid plexus directed brain growth differentially. Therefore, if the fourth ventricular pulsations are overactive, the tentorium is pushed upward and a Dandy-Walker malformation can develop. Conversely, if the supratentorial pulsations are overactive, tentorial migration becomes such that the posterior fossa is small,

allowing the development of a Chiari anomaly as outlined below; in addition, the CSF outlets of the fourth ventricle remain closed, directing the CSF into the patent opening at the obex, thus causing syringohydromyelia.¹⁷

Based on experimental manometric evidence in normal persons and in patients with Chiari malformation, Williams¹⁸ expanded on Gardner's theory by suggesting that Valsalva maneuvers result in epidural venous congestion and intracranial as well as intraspinal rises in pressure, causing fluid to flow both cranially and caudally. Although flow into the cranial compartment meets no resistance, caudal flow is delayed by hindbrain adhesions and outlet obstruction, thus creating a pressure differential between the cranial and spinal compartments. This pressure differential may last a few seconds and cause worsening hindbrain impaction and syringohydromyelia. Heiss et al have shown with intraoperative ultrasound that during systole, the associated syrinx decreases in size, and during diastole, the syrinx grows in size.³⁶ Repeated measurements made after surgical decompression showed equilibration of the pressures in the two compartments; this in turn, correlated with clinical improvement.¹⁸ However, spinal cord cavitation is often acquired (as in posttraumatic syringohydromyelia), and a connection between the cyst and the fourth ventricle is not always present, which raises doubts about the adequacy of this theory. In addition, acquired C1Ms have been extensively reported after multiple lumbar punctures,¹⁹ lumbar-peritoneal shunting,²⁰ and spinal arachnoid shunting,²¹ and also arising spontaneously without external intervention.²² A case report describing a fatal case of chronic tonsillar herniation after a lumbar puncture and lumbar-peritoneal shunt revision in a patient with Crouzon disease is a dramatic example of this point.²⁰ Explanations of the pathophysiology of acquired tonsillar herniation have been mainly based on the pressure differential created by lumbar CSF diversion. One hypothesis states that the siphoning of CSF causes a pressure gradient that directly induces the cerebellum to descend. Another hypothesis attributes the herniation to skull growth arrest secondary to chronic CSF siphoning. In these cases, the growing brain is limited by a small posterior fossa volume.²³ However, these hypotheses do not explain the cases of spontaneous herniation. Amin-Hanjani et al²³ have attempted to explain this phenomenon by hypothesizing that a mismatch in the growth of the bony and neural components of the posterior fossa occurs during development. Because the cerebellum reaches approximately 80% of its adult weight in the first year of life, a small posterior fossa may be limiting enough to induce this rapidly expanding neural structure to herniate. Marin-Padilla and Marin-Padilla²⁴ initially described the small posterior fossa theory in 1981. The treatment of hamster embryos with vitamin A induced mesodermal insufficiency in these animals, leading to underdevelopment of the occipital bone and a small posterior fossa. It was hypothesized that a small posterior fossa would act as a barrier against continued growth of the posterior fossa neural structures, thus pushing these structures downward and upward outside the confines of the fossa. Rachitic patients with bony overgrowth of the posterior fossa (► Fig. 16.10) have a high incidence of C1M. Patients with growth hormone deficiency may have an incidence of C1M as high as 20%.²⁵ Both these groups support a theory that restricted posterior fossa volume will be associated with the development of hindbrain hernias. Lastly, the increased incidence



Fig. 16.10 Operative demonstration of massive cerebellar herniation (elevated with the forceps) over the cervical spinal cord (C4).

of C1M in patients with craniosynostosis lends credence to a small or restricted skull resulting in tonsillar ectopia. C1M is especially observed in patients with synostosis of the lambdoid suture(s).

How can a single theory of pathogenesis explain all the anatomical abnormalities associated with Chiari malformations? Do the different types of hindbrain herniation belong to the same spectrum of malformations and differ only in degree, or are they truly distinct entities with different embryologic etiologies? Osaka et al,²⁶ who found that the neural tube defect occurred before the hindbrain deformity in affected fetuses and embryos, have evaluated the association of Chiari malformations with myelomeningocele. Because the cerebellar vermis develops before the tonsils, an abnormal pressure differential developing in utero would cause abnormal displacement of the vermis and brainstem structures, without any tonsillar involvement. Such a pressure differential could occur with fluid leakage from the myelomeningocele.

McLone and Knepper¹⁵ have advanced a “unified theory” that would explain the cause of the C2M along with most, if not all, of the associated anomalies. This theory is based on the above assumption that the neural tube defect occurs first; all the other manifestations, including the Chiari malformation and hydrocephalus, follow secondarily. Leakage of CSF through the spinal defect causes a lack of distention of the primitive cranial ventricular system. Multiple abnormalities form because mechanical support from normally distended primitive ventricles is a prerequisite for the normal development of the cerebral cortex and overlying skull. In experimental animals, venting fluid from the embryonic ventricular system causes disorganization of the developing cerebral cortex. In addition, the tentorium is left low, which leads to a small posterior fossa, abnormal development of the pontine flexure, and herniation of posterior fossa structures downward through the foramen magnum and upward through the tentorial notch. The lack of distention of

the third ventricle was hypothesized to cause the thalami to remain in apposition, resulting in a large massa intermedia. Even lückenschädel was thought to form because of a lack of distention of the underlying neural mass, a requisite for collagen organization and normal ossification.

In summary, the current best evidence is that the development of a craniospinal pressure gradient across the foramen magnum will cause or hasten the development of a hindbrain hernia. If this occurs after the development of the cerebellar tonsils, they will move through the foramen magnum. If the gradient occurs before the development of the tonsils, in utero, the vermis will be caudally displaced. The gradient results from impaired CSF flow across the foramen magnum. CSF enters the intracranial compartment from the intraspinal compartment easily, but its egress is impeded. There is a vector of force out of the intracranial compartment. This mechanism is responsible for most cases of acquired C1 M, although congenital factors can create this situation, as well. Conversely, intracranial pathology such as mass lesions and hydrocephalus may increase the gradient of intracranial pressure to spinal pressure, causing C1 M. Lumbar–peritoneal shunting, repetitive lumbar punctures, lumbar drainage, and chronic spinal CSF leaks of an iatrogenic nature are all causes of an acquired C1 M.

16.4 Treatment

16.4.1 Chiari 1 Malformations

Surgical Indications

No effective nonsurgical alternative exists for symptomatic patients with C1 M. The benefit of surgery in changing the clinical course of patients with C1 M has been documented in retrospective studies from the past several decades. The immediate relief of symptoms and the objective decrease in the size of syringes following surgical intervention have substituted for precise knowledge of the natural history. The discussion then is not as much about whether patients with hindbrain hernias should be surgically treated, but rather about (1) whether the definition of significant hindbrain herniation should be tightened, (2) the timing of surgery, and (3) the specifics of the operation.

Some basic principles are generally agreed upon. If hydrocephalus coexists or any question of raised intracranial pressure is present, this situation should be resolved before any consideration is given to decompression. The likelihood of a craniocervical decompression resolving appropriate symptoms is 80 to 85%, with minimal operative risk.³ Syringes generally show evidence of decreasing in size or totally resolving within 6 months of surgery. A lack of resolution of symptoms, especially headache, generally indicates improper patient selection. Not all patients with 5 mm of caudal descent of the tonsils and headache will improve with Chiari decompression. The more typical the headache with Valsalva induction, especially if the patient can reproduce the headache consistently with a single maneuver, the greater the likelihood the problem will be resolved. The less typical the pain, especially without a Valsalva-induced component, the less likely surgery will be effective. Between these two extremes, clinical judgment will help guide decision making. We have no experience with repeated decompression for headache if the initial decompression is unsuccessful. When an asso-

ciated syrinx is present and symptomatic, more objective criteria are to be followed. In more than 90% of patients, the syrinx will respond within 6 months both clinically and radiologically. With time, in at least 5 to 10%, a syrinx and symptoms will redevelop. This group, together with the small group that does not respond initially, has a high (>90%) likelihood of responding to a secondary decompression in which resection of one or both tonsils is performed.³ With this in mind, some surgeons have incorporated tonsillar resection with the initial procedure. We have not, reserving the resection of brain for a secondary procedure. Such internal decompression of the tonsils consists of resection to a point of visualization of the inferior aspect of the fourth ventricle without retraction. Alternative steps are simply to coagulate the tonsil and cause it to shrink. If this method is chosen, the surgeon should attempt to minimize trauma/injury to the medial surface of the tonsil as scarring there may be associated with recurrent symptoms. During a secondary decompression, the surgeon must weigh additional bony decompression and dural opening and grafting, resulting in a wider decompression, against the possibility of the development of cerebellar ptosis, or “slump,” which is a serious complication. We have not experienced this problem, undoubtedly because our opening is usually “adequate,” but not excessive. This opening is 22 to 25 mm in width at the foramen magnum and about the same distance in height. Having said that, with recurrent or inadequate clinical outcome, thought should be given to expanding the internal decompression. This maneuver during a second procedure has been helpful in postoperative patients referred to us, as well as in our own initial failures. The internal decompression consists of tonsillar resection to the point of visualization of the inferior aspect of the fourth ventricle without retraction.

An error that we have committed has been in choosing dorsal decompression when some ventral compression coexisted. In defining what is “significant” ventral compression, we propose that when the ventral compression exceeds 9 mm (perpendicular distance from a plane drawn between the basion and the posterior–inferior aspect of C2), a risk in dorsal decompression exists (► Fig. 16.11).²⁷ When more than 9 mm of ventral

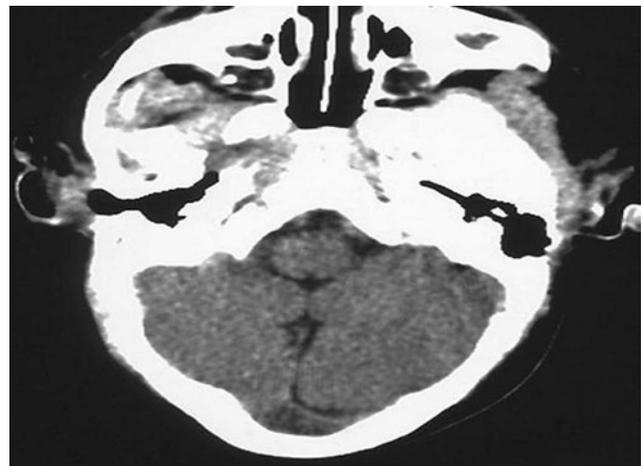


Fig. 16.11 Axial computed tomographic scan of the head through the posterior fossa of a child with vitamin D–deficient rickets and Chiari 1 malformation. Note the small posterior fossa volume due to bony overgrowth.

compression exists but the patient does not have significant medullary symptomatology, a judgment should be made as to the risk for deterioration from dorsal decompression versus the risk for transoral decompression and occipitocervical fusion. When ventral compression is severe, this decision is simple, and transoral decompression is necessary. Spinal instability at the craniocervical junction is rarely present. This should be investigated with flexion–extension X-rays before surgery if any question exists.

In the setting of hindbrain herniation and syrinx, we have not placed a syringopleural or peritoneal shunt in the past two decades. Shunting the syrinx with the necessary myelotomy will result in some sensory loss with possibly additional neurologic difficulties. These shunts will malfunction with a concerning frequency in selected patients, and revision of the system frequently requires replacement of the syrinx catheter or its adjustment. This maneuver has always been of concern because of the risk for significant spinal cord injury.

Patient Selection

Appropriate selection of the patients likely to respond to surgical therapy can be challenging. Surgical indications vary among physicians, especially for subjective symptoms such as headache. A 1998 opinion survey of North American pediatric neurosurgeons concluded that there was widespread agreement to treat patients with a syrinx and progressive scoliosis or symptoms.²⁸ Opinions were mixed on how to manage individuals with asymptomatic syringes. Opinions varied widely on the most appropriate surgical technique. With a lack of objective data comparing various surgical techniques, we will simply outline our approach and record the results.

Acquiring adequate imaging and clinical data is the first step in managing this diverse group of patients. Patients suspected of having C1 M should undergo MR imaging of the brain and entire spine to assess tonsillar ectopia, rule out hydrocephalus, and screen for a syrinx. Cine MR imaging may be used to assess CSF flow at the foramen magnum, but it has been of little use to us in determining indications for operation. This is not to say that we do not believe in the concept of looking, but simply that the currently available software has not proved to be useful in making clinical decisions. The size of the ventricles is assessed as previously outlined, and flexion–extension radiographs of the cervical spine are obtained in the unlikely event that there is instability.

Generally, tonsillar herniation greater than 5 mm is considered abnormal, but not necessarily indicative of the need for treatment. Individuals with less hindbrain herniation and large symptomatic syringes may have functional limitation of the egress of CSF from the fourth ventricle. They may very well benefit from decompression. A large hindbrain hernia may remain asymptomatic for years and in infancy and childhood may progressively become less impressive with time. Hence, the diagnosis and recommendation for surgery for patients with C1 M must be based on both clinical and radiologic criteria.

Once patients are determined to have idiopathic C1 M and hydrocephalus is ruled out, they are divided into two broad categories based on the presence or absence of a syrinx. In our

clinic, the vast majority of patients with a syrinx and significant hindbrain hernia are offered surgical decompression. The more significant the symptoms, the easier it is to justify this position. Patients with a visible central canal and minimal herniation are followed. This strategy is based on the belief that a syrinx is indicative of pathologic forces acting on the spinal cord that should be corrected to prevent permanent cord damage. This approach is not universal; some authors advocate a conservative approach for small asymptomatic syringes.²⁹

In patients without syringes, the situation is much more subjective. A patient with Valsalva-induced occipital headache/neck pain that is easily reproducible, of short duration (seconds to minutes), and life-dominating is at the easiest end of the spectrum for rendering a judgment. Without a clear element of Valsalva induction of the pain, even with impressive degrees of hindbrain herniation, the patient may not benefit from surgery. We do not offer decompression for headache alone without a clear abnormality on MR imaging (caudal descent of the tonsils of > 5 mm and appropriate characteristics of the headache). The most difficult situation we deal with is the child with 5 mm of caudal descent, no syrinx, and severe, life-dominating, diffuse headache unresponsive to medical intervention. In this situation, the family and referring neurologist may repeatedly point to the X-ray report outlining the diagnosis of C1 M. An in-depth discussion with the family regarding the lower likelihood of success in alleviating the headache with surgery may help. Involvement of a medical specialist in headache is frequently of help.

The third group comprises patients who have a wide variety of symptoms and signs. They require more discussion. Symptom complexes may be unique and not appear in standard symptom lists. The infant who is a poor feeder or who has downbeat nystagmus, nasal speech, malignant hiccups, and even rarely essential hypertension may have a hindbrain hernia as the etiology. The challenge with this group is to be able to localize the symptoms to the brainstem and think to perform MR imaging. Patients with medullary dysfunction related to breathing and swallowing should not be given a trial of conservative care before surgical decompression. This may be a more important message for the nonsurgical community.

Surgical Technique

With knowledge that the intracranial pressure is normal and the cervical spine stable, the patient is positioned prone with the neck flexed. This position is held with a pin fixation device. We use pin fixation devices even in young children and infants. The clamp is tightened until tension appears in the anterior fontanel. Care is taken to position the pins in front of the equator of the skull on the dependent half of the skull, forcing the skull into the fixation device. The body is held on the table with tape in small children or with a footboard in older children, and the head is raised until the operative field is parallel to the ground. The incision extends from the C2 spinous process to a point just below the external occipital protuberance. The midline of the posterior cervical musculature is identified by the small amount of fat within it and the muscles separated. Care is taken not to disrupt the muscle insertion superiorly or

inferiorly at C2. Lateral exposure is the width of the spinal canal at C1 and approximately 50% more than that in the occipital region. A suboccipital craniectomy and removal of the posterior arch of C1 are performed, with a realization that the pathology is in the midline. The dorsal dura at C1 is exposed and the foramen magnum until the bone becomes more vertical to the operator. The dura is opened in a linear fashion beginning in the cervical region. Traction stitches are applied to the full thickness of the dura to help control bleeding from the occipital sinus. If necessary, horizontal incisions are made in the dura at the level of maximum constriction (usually the foramen magnum) to allow additional relaxation. The arachnoid is opened off the midline and clipped to the dura with metal clips, in effect fusing the two layers. The fourth ventricle is explored by separating the cerebellar tonsils. Adhesions that prevent separation of the tonsils are lysed. The avascular floor of the fourth ventricle is appreciated. A pericranial graft is harvested through a separate incision that is large enough to provide a tension-free dural patch.

There are many variations of this technique, with numerous authors advocating bony decompression alone or dural opening without arachnoidal disruption. Each of these approaches has its champions. Our purpose here, without any randomized trial data, is to describe how this procedure has evolved in our practice. The justifications for each step are generally a complication of our own or of one of our colleagues that we are trying to avoid.

16.4.2 Chiari 2 Malformations

Surgical Indications and Technique

The natural history of patients with a C2 M seems to be age-dependent. In the series of Pollack et al³⁰ of 25 patients with symptomatic C2 M, 13 neonates presented with symptoms of brainstem dysfunction before 3 months of age and 12 patients presented after this period. In the older group, no patient died or had a poor outcome. Of the neonates, 23% died, 16% had a poor outcome, and the remainder had a good outcome. In the prospective series of Pollack et al,³¹ approximately 77% of symptomatic patients recovered normal or nearly normal brainstem function following decompression (occipital craniectomy and laminectomy). A presentation with bilateral vocal cord paralysis was found to have the worst prognosis. The results of Pollack et al are contrasted with the experience of Bell et al,³² whose success rate was only 30%. In our own experience, the results are directly related to how carefully one looks for symptoms and signs. At least one-third of patients with a closed myelomeningocele and shunted hydrocephalus will develop medullary dysfunction. This becomes progressively less likely the older the patient becomes. Before 3 months of age, symptoms may very well be life-threatening.

What has become increasingly clear to us is the relationship of symptoms of medullary dysfunction to shunt function. The adage "It's a shunt malfunction until proven otherwise" is correct in the vast majority of patients, and the number of C2 M decompressions we perform has drastically decreased since this realization. The criteria we use to determine shunt

malfunction is as follows. The patient with myelomeningocele who presents with medullary dysfunction and a brain image that may very well be improved from the preshunt image is still considered to have shunt malfunction as the reversible cause of the symptoms. Even patients with normal or small ventricles are brought to the operating room for surgical inspection of the shunt when medullary symptoms are present. In addition, the infant or myelodysplastic child who experiences neck pain is assumed to have a shunt malfunction until it is proved otherwise.

Intraoperatively, the shunt is tested for ventricular catheter flow and peritoneal catheter runoff; in addition, ventricular catheters that are adherent within the ventricular system are removed and repositioned. This will require judgment both as to how vigorous to be in removal of the old catheter and as to the technique to use in reinserting a catheter in a small ventricular system. We have found that a small neuroendoscope that fits within the ventricle is of great value in positioning the new catheter with a high accuracy rate.

With use of this primary focus on shunt function, our incidence of C2 M decompression has drastically decreased. On rare occasions (once in 7 years), a patient with refractory symptoms will have what appears to be a functioning shunt with progressive symptomatology. In that case, C2 M decompression is justified.

Once the decision is made to perform a C2 M decompression, spinal stability is again ensured with flexion–extension X-rays. The patient is positioned prone with the head held in a flexed position. We use a pin fixation device even in infants and young children; however, the clamp is tightened only enough to hold the head without significant tension being translated to the anterior fontanel. The head of the bed is elevated and the patient fixed to the bed.

An incision is made from the mid occiput to the lower extent of the herniated cerebellar vermis. This point is usually marked by a small bright enhancing mass representing the choroid plexus on enhanced MR imaging. In the patient with C2 M, the choroid plexus maintains its embryonic position at the outlet of the fourth ventricle and does not rotate into the roof of the fourth ventricle (► Fig. 16.12). The choroid marks the point of dissection for entering the fourth ventricle and is an important landmark. It is critical that the position of the torcular be assessed preoperatively. Frequently, the dural sinus system is low, sometimes approaching the foramen magnum. If the operator removes some occipital bone and opens the dura in the standard manner, it is entirely possible that a surgical misadventure will ensue. The amount of suboccipital bone that it is necessary to remove is usually small, and then only at the rim of the foramen. The dura is opened in the midline and the choroid plexus sought. The brainstem and upper spinal cord are frequently hyperemic from chronic displacement and ischemia. At times, the operator will confuse the bottom of the medullary kink for the opening into the fourth ventricle. Dissection between the kink and the upper cord should be avoided. On occasion, intraoperative ultrasound will be helpful in locating the ventricle and determining a point of entrance. Once the fourth ventricle is identified, the opening into it is performed, with visualization of the relatively avascular floor of the fourth ventricle. Again,

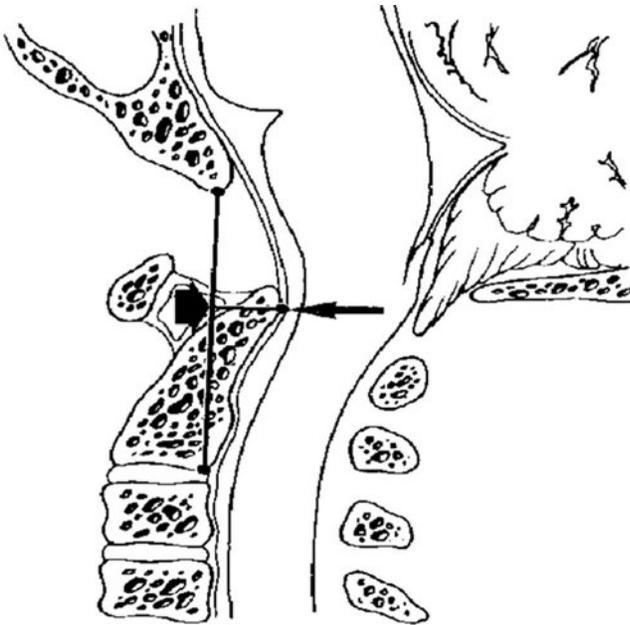


Fig. 16.12 Schematic drawing showing how we have quantified ventral compression in Chiari 1 malformation. (Grabb PA, Mapstone TM, Oakes WJ. Ventral brain stem compression in pediatric and young adult patients with Chiari I malformations. *Neurosurgery* 1999;44:520–552. Printed with permission.)

the dura is grafted with pericranial fascia. In planning for this decompression, one should minimize the bony removal in an attempt to avoid the postoperative kyphosis that is sometimes seen when a large syrinx is present in the cervical region.

These procedures are much more difficult than a standard C1 M decompression and are usually done in an infant or child who has serious neurologic compromise. The experience of the surgeon is especially important in minimizing complications and ensuring an adequate decompression.

16.4.3 Complications of Surgery

Chiari 1 and 2 Decompressions

Posterior fossa decompression is relatively safe but not without potential complications. Direct vascular and neural injury, pseudomeningocele, vascular lake bleeding, CSF leaks, and meningitis are well recognized. Less common complications include unrecognized occipital–cervical instability, acute postoperative hydrocephalus secondary to infratentorial hygromas, and anterior brainstem compression from a retroflexed odontoid.^{3,33} A complication unique to posterior fossa craniectomies is cerebellar slump or ptosis, which results from extending a craniectomy and dural grafting so far laterally and superiorly that the cerebellum herniates through the craniectomy defect. Cranioplasty to buttress the cerebellum into place is the most definitive treatment. Complications in our series of 500 patients were infrequent and included acute postoperative hydrocephalus requiring temporary external ventricular drainage and severe anterior brainstem compression requiring urgent transoral odontoidectomy. Meningitis or cerebellar slump was not observed.

There were no deaths. Recurrence of symptoms after a C2 M decompression is sometimes due to hydrocephalus or syringomyelia. Bone regrowth into the area of decompression may occur if the decompression is performed in very young children and has been associated with recurrent symptoms.³⁴

16.4.4 Results and Prognosis

Chiari 1 Malformations

The literature is replete with conflicting reports comparing variations of the posterior fossa decompression procedure for the C1 M. Without a large, long-term prospective study, no firm conclusion can be made regarding the different techniques. The likelihood of such a study appears remote given the relatively low incidence of the disease process, the relatively minor variations in technique, and the significant obstacles one encounters in organizing such a study. We are therefore forced to draw conclusions from our own experience and a review of the literature.

With an incomplete natural history, surgical data accumulated from a series of retrospective studies that claim to improve upon the natural history should be looked at cautiously. With an average of 7 years of follow-up, patients who presented with Valsalva-induced headache and neck pain had a very high likelihood of remaining asymptomatic.³ Children with symptomatic syringomyelia had a better than 95% likelihood of the syrinx remaining small or insignificant and the symptoms remaining stable or improved. In our series, this required a second procedure in the vast minority of patients with a syrinx. Scoliosis of more than 50 degrees, foot deformity, and other orthopedic changes involving bone generally remain the same. Children with neurologic deficits generally improve to a functionally normal status if operated upon in a timely manner. We again emphasize our prejudice for re-exploring the posterior fossa rather than performing myelotomy and any type of drainage of the syrinx.

Longer-term follow-up will need to be done to confirm these data, but in general the outlook for a child with a symptomatic C1 M is excellent. This implies appropriate patient selection. The adolescent patient with non-Valsalva-induced headache and a rounded 3-mm caudal descent of the tonsils does not have the same likelihood of complete resolution of the headache and pain after surgery.

Chiari 2 Malformations

The natural history of patients with this problem can be quite serious, with medullary symptoms still the leading cause of death in this population with treated myelomeningoceles. Early surgical intervention in a symptomatic infant or child is widely accepted, although only a few studies exploring the role of decompression in C2 M are available. Neonates and young infants displaying symptomatic C2 M require urgent evaluation and intervention. A more casual approach is likely to result in fixed deficits of swallowing and breathing. We cannot overstate attention to the function of the shunt; a simple comparison of the CT scans is inadequate in our view. Still, very young infants may do very poorly and succumb despite all efforts.

Pearls

- Although unique presentations of the Chiari 1 malformation occur, patients should be cautioned that surgical outcomes are less predictable.
- Valsalva-induced headache resulting in neck and occipital pain in this group is one of the most predictable preoperative symptoms to resolve following surgery.
- Posterior fossa decompression should occur in the midline and need not extend more laterally than the width of the foramen magnum.
- It is critical to avoid contamination of the subarachnoid space with blood during posterior fossa decompression.

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17 Encephaloceles, Meningocele, and Dermal Sinuses

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Substantive congenital anomalies exist that affect the craniofacial skeleton and represent defects in scalp, bone, meninges, and brain development. A wide spectrum is seen in the clinical setting, ranging from mild and nonvisible bony defects to severe cases of anencephaly (absence of the brain) and acrania (absence of the calvaria and brain). Anencephaly presents with acrania plus protrusion of a significant portion of the brain covered with a highly vascular epithelium that is tightly adherent to the underlying cerebral tissue. Amniotic bands in utero are thought to wrap around the cranial base, causing disruption of normal growth and leading to exencephalus and “nonanatomical” encephaloceles. Encephaloceles are a group of malformations characterized by calvarial and dural defects with extracranial herniation of leptomeninges, brain, and cerebrospinal fluid (CSF). In meningocele, the calvarial defect is associated only with the herniation of leptomeninges and CSF. Cranium bifidum occultum is a midline or paramedian calvarial defect that is not associated with brain, meningeal, or CSF prolapse.

Encephaloceles and meningocele have a common genetic background, but they are distinctly different and separate entities. The various types of meningoencephaloceles differ considerably in pathology, clinical presentation, racial and geographic distribution, treatment plans, and prognosis. Our goal in this chapter is to present a concise and comprehensive review of these craniofacial anomalies.

17.1 Encephaloceles

17.1.1 History

The earliest recorded documentation of encephaloceles can be found in ancient sculptures and medieval art. These abnormalities were commonly depicted in individuals portrayed as demons and monsters. The earliest recorded descriptions can be credited to Forestus (1590).¹ A century and a half later, Friderici (1737)² published his findings of an autopsy performed on a stillborn with a severe form of Robert’s syndrome and associated anterior encephalocele. The first monograph on encephaloceles was written by Corvinus in 1749.³ The pathogenesis of nasal frontal encephaloceles has been a subject of debate and controversy over the years. Multiple theories have been proposed to explain the development of these congenital anomalies.

In the 19th century, Saint-Hillaire (1827)⁴ published a theory based on experimental work on chicken embryos. He proposed that adhesions resulting from intrauterine pressure caused a malformation known as *hernie du cerveau* (“hernia of the brain”) to form between the brain anlage and germinal membranes, which led to an arrest in the development of the anterior cranial vault. Herniation of the brain thus occurs through this pathologic opening (► Fig. 17.1).

Several years later, Himly (1829)⁵ and Serres (1832)⁶ proposed that hernias formed through normally present bony channels, as opposed to a mild developmental formation through abnormal bony slits. In 1854, Spring⁷ hypothesized that encephaloceles arose as a consequence of various forms of ventricular dilation. In 1850, Rokitansky⁸ theorized that “congenital



Fig. 17.1 Illustration of a clinical case showing an infant with a large nasofrontal encephalocele. (From Hutchinson, 1875. Courtesy of Dr. James T. Goodrich.)

herniation of the brain was caused by an extreme increase in organ bulk.” In 1868, Klementowsky⁹ proposed that these congenital anomalies were secondary to bone-related pathologic processes such as cranial tabes, rickets, and syphilis. Ankermann¹⁰ in 1882 continued to attribute these lesions to hydrocephalic states. Schmidt¹¹ in the 1900s blamed olfactory bulb remnants as the primary cause of encephaloceles (► Fig. 17.2a,b).

17.1.2 Classification

Several classification schemes have been proposed by multiple authors in the past, leading to confusion in the nosologic categorization of the lesions.^{12–17} A currently well-accepted classification is based on the anatomical location of the skull defect.¹⁸ Primary encephaloceles are those lesions that either are present at birth or have a congenital substrate. Secondary encephaloceles are acquired lesions that are most commonly the result of trauma or surgery.

Primary encephaloceles are divided into three major types: cranial vault, frontoethmoidal, and basal. Cranial vault encephaloceles can occur anywhere in the skull, and in North America they most commonly present in the occipital region (see box “Classification of Encephaloceles (p.206)”). Atretic encephaloceles are forme fruste encephaloceles; they characteristically

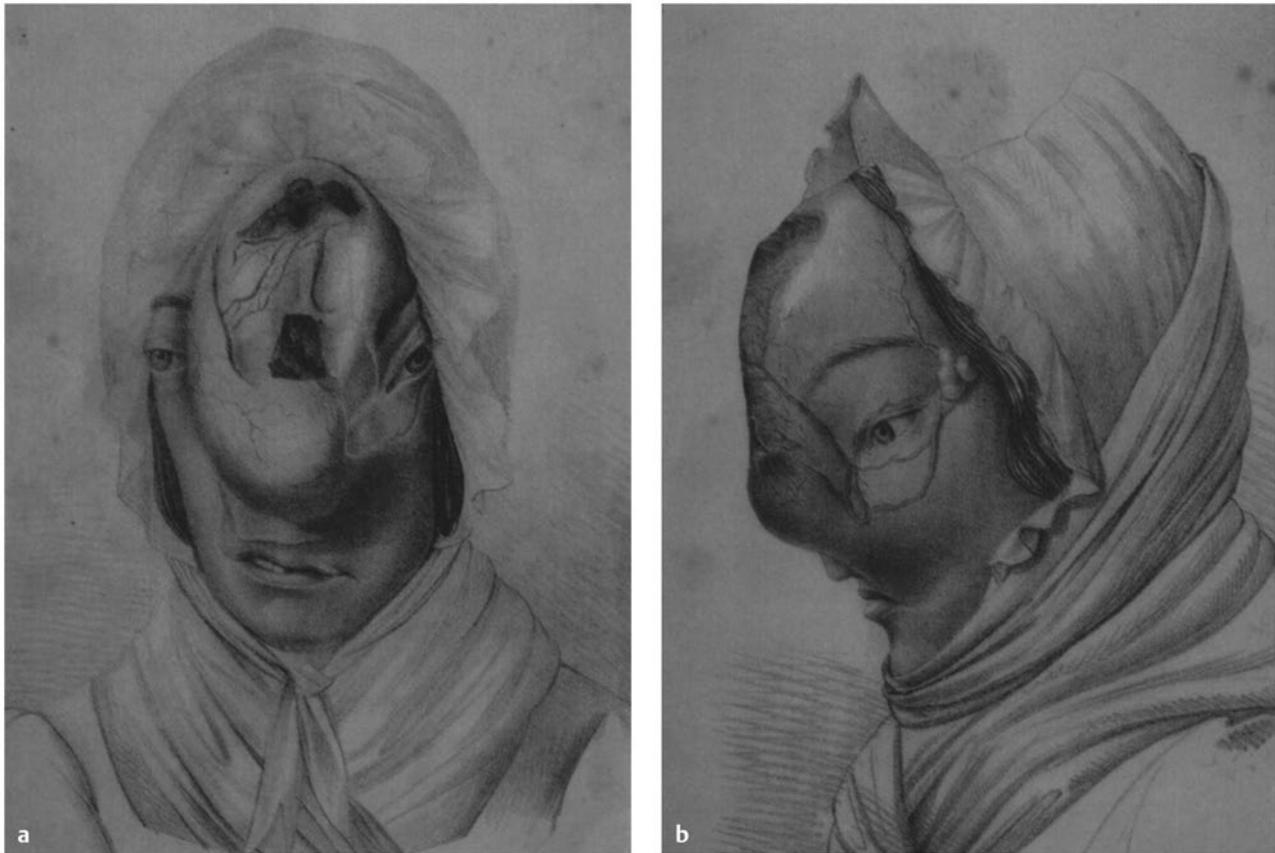


Fig. 17.2 (a) An adult with a frontal lesion consistent with a large sincipital encephalocele. (b) An adult with a frontal lesion consistent with a large sincipital encephalocele. (From Chelius, 1831. Courtesy of Dr. James T. Goodrich.)

present as small, noncystic nodular or flat lesions located in the midline near the vertex (parietal type) or anterior to the inion (occipital type) (► Fig. 17.3, ► Fig. 17.4a,b). The overall incidence of encephaloceles is approximately 0.8 to 3.0 per 10,000 live births,^{19–22} and when compared with their spinal counterparts, encephaloceles account for approximately 10 to 20% of all cases of craniospinal dysraphism. Encephaloceles comprise approximately 10 to 15% of all neural tube defects.

Classification of Encephaloceles

- Primary
 - Cranial vault
 - Occipital
 - Cervico-occipital
 - Interparietal
 - Temporal
 - Interfrontal
 - Anterior fontanel
 - Posterior fontanel
 - Frontoethmoidal (sincipital)
 - Nasofrontal
 - Nasoethmoidal
 - Naso-orbital
 - Basal
 - Transethmoidal

- Transsphenoidal
- Sphenoethmoidal
- Sphenomaxillary
- Spheno-orbital
- Sphenopharyngeal
- Temporal
- Posteroinferior (endaural)
- Anteroinferior
- Cranioschisis
 - Acrania: exencephaly
 - Cranial: upper facial cleft
 - Basal: lower facial cleft
- Secondary
 - Traumatic
 - Postsurgical
 - Inflammatory
 - Neoplastic

17.1.3 Epidemiology

The incidence of encephaloceles varies worldwide with geographic location and race.²³ Occipital encephaloceles are the most common type in North America and western Europe, with an incidence varying between 1 in 3,000 to 1 in 10,000 live



Fig. 17.3 Newborn male with a small, pulsating bony defect and an abnormally colored scalp. A small amount of cerebral tissue herniates through the opening.

births; they comprise ~85% of all encephaloceles.^{24–26} Seventy percent of occipital encephaloceles occur in females, and 15 to 20% are found in association with neural tube defects.^{27,28} In contrast, anterior encephaloceles occur with greater frequency (1 in 3,500 to 1 in 5,000 live births) in Southeast Asia (Thailand, Indonesia, Burma, Philippines, Malaysia), parts of Russia, and central Africa.^{23–33} The incidence of anterior encephaloceles in North America is estimated to be 1 in 35,000 live births. Basal encephaloceles are much less common and comprise fewer than 10% of encephaloceles.³⁴ Temporal encephaloceles are extremely rare malformations and are thought to comprise fewer than 1% of cerebrospinal malformations.^{35–37} The true incidence of encephaloceles secondary to trauma or surgery is not known.

17.1.4 Associated Anomalies

An encephalocele may present as a single isolated congenital anomaly or in association with other anomalies to comprise a syndrome or association (► Table 17.1).²⁸ Encephaloceles are most commonly associated with Meckel syndrome and amniotic band syndrome.³⁸ Meckel syndrome consists of occipital encephaloceles, polydactyly, polycystic kidneys, holoprosencephaly, micro-ophthalmia, retinal dysplasia, cardiac anomalies, orofacial clefts, and other anomalies. Occipital encephaloceles were found to occur in 39 of the 49 cases tabulated by Meckel and Passarge.³⁹

Amniotic band syndrome occurs because of amniotic tissue bands that form in utero and lead to the constriction of fetal parts and disruption of normal development (► Fig. 17.5). Most commonly affecting limbs or digits, these bands can become directly attached to the cranium or face, producing “nonana-



Fig. 17.4 (a) Lateral view of a child with an atretic encephalocele. A small cranial defect allowed passage of a gliotic tract associated with abnormally developed skin. (b) Scalp marks for proposed incision to resect an atretic encephalocele. No spinal fluid is associated with this lesion, which was fully resected with excellent long-term effects.

Table 17.1 Syndromes associated with encephaloceles

Syndromes	Prominent Features	Etiology
Occipital encephaloceles		
Meckel syndrome	Polydactyly, polycystic kidneys, holoprosencephaly, micro-ophthalmia, retinal dysplasia, cardiac anomalies, orofacial clefts, ambiguous external genitalia, other abnormalities	Autosomal-recessive
Pseudo-Meckel syndrome	Arrhinencephaly, absent corpus callosum, Arnold-Chiari defect, no evidence of retinal dysplasia, cleft palate, congenital heart defects, accessory spleen, clubfoot, hallux hammer toes	t(3p+)
Chemke syndrome	Hydrocephaly, agyria, absent cortical laminar structure, cerebellar dysgenesis, retinal dysplasia, corneal opacities, cataracts	Autosomal-recessive
Cryptophthalmos syndrome	Extension of forehead skin to cover one or both eyes, unusual hairline, ear anomalies, notching of the nasal wings, soft tissue syndactyly of hands and/or feet, genital anomalies	Autosomal-recessive
Knobloch syndrome	High myopia, vitreoretinal degeneration, retinal detachment, meningocele, normal intelligence	Autosomal-recessive (presumed)
von Voss syndrome	Aplasia of the corpus callosum, hypoplastic olives and pyramids of the medulla oblongata, phocomelia, urogenital anomalies, thrombocytopenia	
Warfarin syndrome	Nasal hypoplasia, bone stippling, limb shortening, low birth weight, optic atrophy, mental retardation, seizures, hydrocephaly	Warfarin during pregnancy
Frontal encephaloceles		
Frontonasal dysplasia	Ocular hypertelorism, widow's peak, anterior cranium bifidum occultum, widely set nostrils with lack of elevation of the nasal tip, notching of nostrils, other abnormalities	Most cases sporadic, some familial, probably etiologically heterogeneous
Amniotic band syndrome	Ring constrictions and amputations of digits or limbs, distal syndactyly, irregular or asymmetric encephaloceles, microcephaly, micro-ophthalmia, bizarre orofacial clefts, other facial disruptions, tissue bands, various other anomalies	Aberrant tissue bands

Source: Adapted from Cohen MM, Lemire RJ. Syndromes with cephalocele. *Teratology* 1982;25:161–712.³⁸

tomical” encephaloceles. The lesions are unusual because they have irregular surfaces, are asymmetrically placed with respect to the midsagittal plane, and have multiple sites of involvement (► Fig. 17.6, ► Fig. 17.7, ► Fig. 17.8, ► Fig. 17.9). Chemke syndrome is characterized by occipital encephaloceles, hydrocephalus, agyria, retinal dysplasia, corneal opacities, and cataracts.⁴⁰ Cryptophthalmos syndrome involves extension of the forehead skin to cover one or both eyes, unusual hairline, ear abnormalities, notching of the nasal wings, soft tissue syndactyly of hands and feet, genital anomalies, and a 10% incidence of occipital encephaloceles. It is inherited as an autosomal-recessive trait. Knobloch syndrome presents with myopia, vitreoretinal degeneration, retinal detachment, and occipital meningoceles.⁴¹ von Voss syndrome involves aplasia of the corpus callosum, hypoplastic olives and pyramids of the medulla, phocomelia, urogenital anomalies, thrombocytopenia, and occipital encephaloceles. Warfarin syndrome has been associated with the ingestion of warfarin during pregnancy. It presents with nasal hypoplasia, bone stippling, limb shortening, low birth weight, optic atrophy, mental retardation, seizures, hydrocephalus, and occasionally occipital encephaloceles.

Associated anomalies (see box “Associated Anomalies Seen in Patients with Encephaloceles (p.208)”) include absence of the corpus callosum, optic nerve abnormalities, cleft lip, cleft pal-

ate, Tessier facial clefts, craniosynostosis, Dandy-Walker cyst, Chiari malformations, ectrodactyly, hemifacial microsomia, hypertelorism, Klippel-Feil anomalies, myelomeningoceles, and anophthalmia.³⁸ Hydrocephalus is relatively common in patients with occipital encephaloceles, and the incidence may be as high as 65% (► Fig. 17.7).⁴² In contrast, hydrocephalus is seldom seen in patients with nasofrontal encephaloceles.

Associated Anomalies Seen in Patients with Encephaloceles

- Tessier facial cleft
- Craniostenosis
- Dandy-Walker cysts
- Chiari malformations
- Ectrodactyly
- Hemifacial microsomia
- Hypothalamic–pituitary dysfunction
- Iniencephaly
- Klippel-Feil syndrome
- Myelomeningocele
- Hypertelorism
- Optic nerve abnormalities
- Holoprosencephaly



Fig. 17.5 T1-weighted gadolinium-enhanced coronal magnetic resonance image shows herniating cerebral tissue with a large meningocele and large vascular channels secondary to amniotic bands in utero.



Fig. 17.7 Lateral view of a patient with a large paramedian encephalocele. Although most of the lesion was covered with skin, the distal end leaked cerebrospinal fluid and had a thin neovascularized membrane.



Fig. 17.6 A newborn girl with a large parietal encephalocele secondary to amniotic band syndrome. Eccentrically located lobulated mass was associated with cleft lip and palate and with amputated feet and digits.

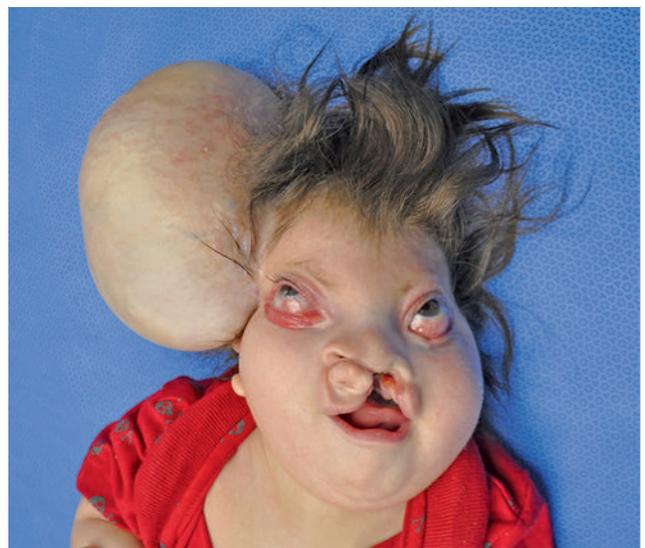


Fig. 17.8 Ten-month-old boy with a large right parietal encephalocele and amniotic band syndrome. Note results of the bands: damage to ear and eyelids, cleft lip and palate.



Fig. 17.9 Highly disorganized encephalocele secondary to amniotic bands.

17.1.5 Occipital Encephaloceles

The etiology of occipital encephaloceles is not well understood, but these anomalies have been correlated with maternal low-folate levels and the use of vitamin A and sodium arsenate. In North America, occipital encephaloceles are the most common type seen clinically and account for approximately 80% of these lesions. The diagnosis is now commonly made with routine prenatal ultrasonography, which helps guide the treatment plan. Given the common association of multiple intracranial anomalies, complete examination of the patient's cranial vault and cervical spine should be undertaken with magnetic resonance (MR) imaging. Although the diagnosis of occipital encephalocele is usually obvious at birth, subtle brain herniations may require a high level of suspicion. Occipital encephaloceles can be located high in the occipital squama or lower at the level of the foramen magnum level; they may even involve the upper cervical spinal levels.

Clinical Presentation

The presence of an occipital encephalocele is obvious at the time of birth, and many of these lesions are now being diagnosed in utero with ultrasonography. Vaginal delivery may be possible with relatively small lesions, whereas larger encephaloceles may necessitate cesarean section. The clinical presentation may vary significantly, depending on the size and contents of the lesion. Infants who have small encephaloceles with little or no herniating brain may act normally, with adequate breathing and normal neurologic examinations. Almost all lesions are fully covered with skin and can be electively repaired. Larger masses may be associated with neurologic deficits: cranial nerve abnormalities, poor sucking and

feeding, spasticity, blindness, and developmental delay. Patients may present with large sacs and microcrania. Associated neural tube defects may be seen in 15 to 20% of the patients.¹⁶ Reported associated congenital malformations include hypoplastic left cranium, bilateral clinodactyly, web neck and micrognathia, thyroglossal cyst, and external annular dermoids.⁴²

Pathology

Encephaloceles are believed to result from the failure of separation of the surface ectoderm from the neuroectodermal elements. The result is a bony defect in the skull that permits herniation of neural elements as well as CSF. The pathology of these lesions directly correlates with their site and location. Small lesions, located in the subtorcular area, may have only CSF and gliotic nonfunctional tissue. Larger masses with bony defects involving the entire occiput and upper cervical levels may have massive infra- and supratentorial brain herniation. The sites of encephaloceles vary significantly. They are often large: larger than 20 cm (16%), 15 to 20 cm (14%), 10 to 15 cm (12%), 5 to 10 cm (30%), and smaller than 5 cm (28%).⁴² The occurrence of associated hydrocephalus varies with published series: 16%,⁴² 36%,²⁵ 50%,⁴³ and 65%.⁴⁴ The skull base may be deformed, and microcephaly has been reported in from 9 to 27% of cases.²⁰ The falx and tentorium are often in an abnormal anatomical position. Bony defects may also vary in size and extent; they may involve just the occipital bone or may include the posterior elements of adjacent vertebrae and even extend superiorly, above the inion. The contents of the sac may be extremely variable. Simpson et al reported that 32% of the patients' lesions contained recognizable cortex, 11% contained cerebellum and fourth ventricular structures, and 20% contained glial nodules. The brainstem may be partially or completely herniated. Thalami were found in 20% of the cases.²⁸ Postmortem examinations^{24,27} have revealed multiple abnormalities, including a small posterior fossa, hypoplastic falx and tentorium, and asymmetric herniation of the cerebral hemispheres ranging from an occipital pole to an entire hemisphere (see box "Associated Findings in Patients with Occipital Encephaloceles (p.211)"). The intracranial contents tend to shift posterocaudally, leading to frontal lobes occupying variable portions of the middle fossa and temporal lobes partially displaced into the posterior fossa (► Fig. 17.10a,b). Notable distention of the ventricular system, optic pathways, corpus callosum, and hypothalamus has been noted. The posterior fossa shows the most remarkable anomalies, with marked brainstem distortion that is often seen as an s-shaped kink (► Fig. 17.11). The cerebellum may be rudimentary and associated with cleftlike fissures extending into the dorsal brain stem from the fourth ventricle. The "inverse cerebellum" described by Padgett⁴⁵ shows ventral protrusion of the cerebellar hemispheres to envelop the anterior lateral aspects of the brainstem, with vermian agenesis or hypoplasia and brainstem kinking. The fourth ventricular roof opens into the sac, leading to a "fourth ventriculocele."

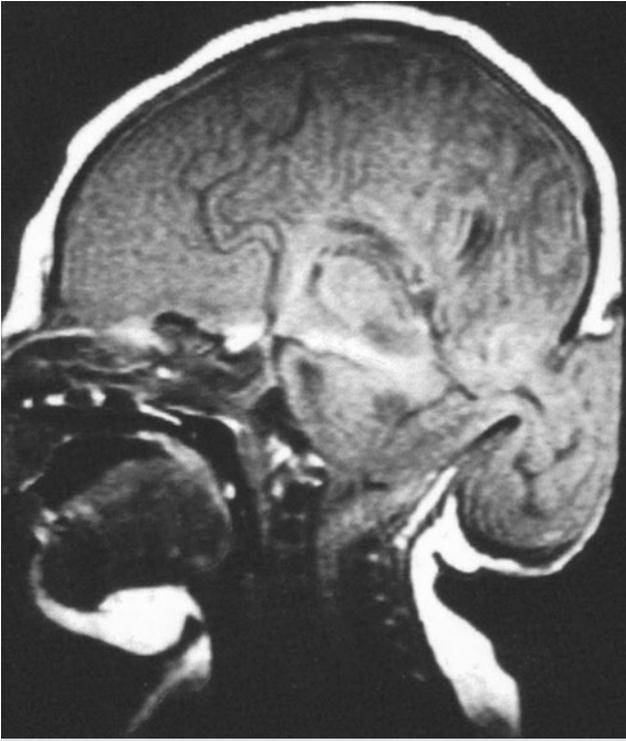


Fig. 17.10 Sagittal magnetic resonance image demonstrates a large amount of herniating cerebellar tissue, along with occipital lobe, through a small cranial defect. Coronal magnetic resonance image showing a large meningocele associated with the encephalocele in.

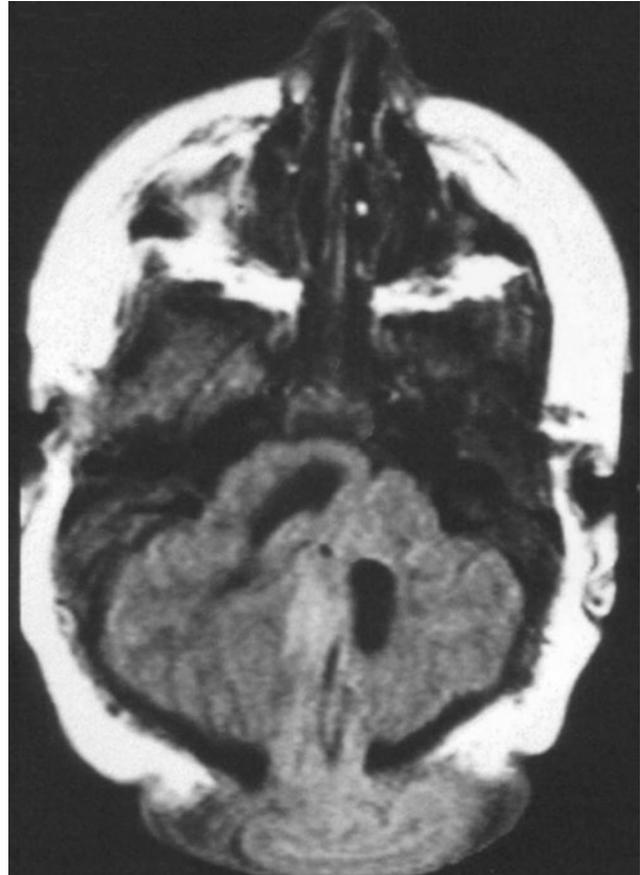


Fig. 17.11 Axial T2-weighted magnetic resonance image of a patient with an occipital encephalocele shows marked dysplasia of the posterior fossa contents.

Associated Findings in Patients with Occipital Encephaloceles

- Brainstem kinking
- Inversion of the cerebellum
- Temporal lobe herniation
- Occipital lobe herniation
- Dysgenesis of the cecum
- Dysgenesis of the vermis
- Corpus callosum dysplasia
- Thalami fusion
- Hydromyelia
- Hydrocephalus

Prognostic Factors and Outcomes

The prognosis and long-term outcome for patients born with occipital encephalomeningoceles are directly proportioned to the amount of neural tissue found in the sac and the severity of the associated neural anomalies. The infant who has only CSF or small nodules of dysplastic neural tissue in the sac has a relatively good chance of attaining normal or nearly normal neurologic and physical development. Patients with few anomalies and a small amount of neural herniation will have approximately a 53% chance of being physically and mentally normal, a 28% chance of normal intelligence but physical impairment, and a 19% chance of mental retardation.²² Conversely, the greater the neural involvement and number of associated neural

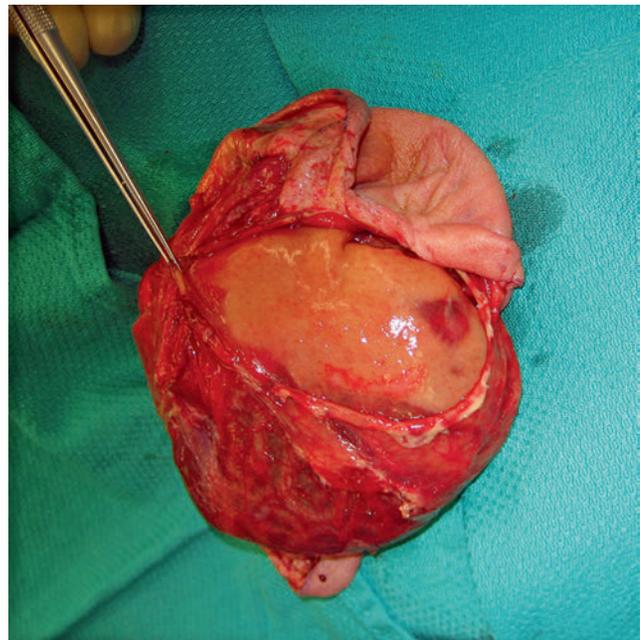


Fig. 17.12 Occipital encephaloceles can present with large amounts of herniated abnormal cerebral tissue. This intraoperative photograph shows an infant with such a lesion and a cortex without a gyral-sulcal pattern.

abnormalities, the greater the rate of mental retardation and poor outcomes. When all patients with occipital encephaloceles are considered, approximately 17% will be normal and 83% will be significantly mentally and physically impaired.²² The appropriate treatment of hydrocephalus plays an important role in the long-term outcome of these patients.⁶⁶

Surgical Treatment

Unless the sac has ruptured and there is concurrent leakage of CSF, surgical repair may be done electively (► Fig. 17.13). The patient is placed prone on an appropriately padded cerebellar horseshoe headrest (► Fig. 17.14a). A single dose of an antibiotic (first-generation cephalosporin) is given before induction. The occipital and upper cervical areas are prepared and draped, with application of povidone-iodine solution. If a large sac is present, it may be elevated with grasping forceps by an assistant to allow complete skin preparation. Using a very low-level (15-W) monopolar electrocautery, the surgeon creates a plane of dissection between the junction of “normal” skin and epithelialized skin. This plane is carefully followed circumferentially and toward the neck of the encephalocele (► Fig. 17.14b,c). A transverse incision is extended to expose the underlying bone and bony defect. A dissection plane is developed between the dura and the skin. Entrance into the dome of the sac will allow CSF to drain and the contents of the sac to be explored. At this point, careful examination of the encephalocele should help guide the surgeon on the proper surgical approach. If the herniating mass is deemed to be composed of fibrous, gliotic, nonfunctional tissue, a decision to transect the mass flush with the skull can be safely made. Some authors have advocated “expansion cranioplasties” to accommodate large amounts of herniated neural tissue. If the herniated tissue is deemed “viable” or resembles normal cerebral architecture, it should be saved, and the expansion cranioplasty technique should be employed.



Fig. 17.13 Newborn female infant with a very large occipital encephalocele.

Barrel stave osteotomies can be created with a drill and expanded outward. The open end of the encephalocele can then be covered with full-thickness calvarial grafts from the surrounding parietal bones (► Fig. 17.15a–c). This maneuver will provide complete osseous coverage of the encephalocele area. However, it should be done only in young infants who are fully capable of regenerating new calvarial bone at the donor site. Another technique uses tantalum mesh to create an extracranial compartment to enclose the neural elements.⁴⁶ The mesh is attached to the periphery of the skull defect. As the intracranial pressure increases, the calvaria is forced to expand, and the mesh is gradually imbricated with the skull by daily digital compression. Another approach is simply to close soft tissues over the neural mass and perform a revision as a second stage.⁴³ A ventricular volume reduction technique has been proposed by Oi et al⁴⁷ to deal with this problem. Using the associated hydrocephalic state, they do a first-stage procedure that involves closing the encephalocele defect with a dural patch graft. The repaired dura allows the intraventricular pulse pressure to produce ventriculomegaly. Once hydrocephalus develops, a ventriculoperitoneal shunt is placed to allow transposition of the herniated brain into an enlarged intracranial cavity.⁴⁸ However, despite attempts at preserving neural tissue by these techniques, profound morbidity continues to be associated with large occipital encephaloceles.

If the skull defect is small (pedunculated encephalocele), no specific management of the bone defect is necessary. Whenever large calvarial defects are present, a simple way to manage them is to extend the skin opening into adjacent parietal regions. A full-thickness craniotomy fitting the shape of the skull defect may be harvested and transposed. The donor site contains osteogenic dura that will ossify and create new bone within 2 to 6 months (► Fig. 17.16a–f). Another acceptable method for dealing with large calvarial defects is to close the encephalocele first, and then later (when the child is about 2 years old) proceed to an autologous cranioplasty with a split-thickness calvarial graft. Hydroxyapatite bone cement (Bone Source; Howmedica Leibinger, Dallas, TX) is commercially available for the closure of cranial defects up to 25 cm.¹³ The cement is composed of tetracalcium phosphate and dicalcium phosphate powder reactants that, when mixed with water, lead to the isothermic formation of a solid implant composed of carbonated hydroxyapatite. This compound has been used successfully to reconstruct posterior fossa calvarial defects⁶⁸ and perhaps should be considered for reconstructing small encephalocele defects in selected patients. Yet another method for closing a skull defect associated with an encephalocele involves the use of HTR-PMI, which is a combination of PMMA (poly-methylmethacrylate) and PHEMA (poly-hydroxyethylmethacrylate) and has a rigidity similar to that of bone (W. Lorenz Surgical, Jacksonville, FL). A proprietary computed tomographic (CT) scan protocol is used to produce a custom-fitting implant.

17.1.6 Anterior Cranial Fossa Encephaloceles

Various classifications have been proposed for categorizing encephaloceles located in the anterior cranial fossa. Sincipital encephaloceles are those lesions that are associated with the skull



Fig. 17.14 (a) The patient is placed prone in a padded cerebellar horseshoe headrest. Care must be taken not to allow the encephalocele to move inadvertently and cause torsion of the cerebral contents of the posterior fossa. (b) A plane of dissection is developed between the scalp and the encephalocele. A vascular scalp is often seen, and care must be taken not to violate the galea and cause significant blood loss. (c) Successful resection of the encephalomeningocele of the patient in ► Fig. 17.13.

defect at the foramen cecum, anterior to the cribriform plate. Suwanwela and Suwanwela proposed the most useful and widely accepted classification of sincipital encephaloceles in 1972.¹⁸ They classified these lesions as nasofrontal, nasoethmoidal, naso-orbital, and interfrontal encephaloceles. Basal encephaloceles are those lesions that protrude through the floor of the anterior cranial fossa (cribriform plate, planum

sphenoidale). These lesions have been classified as sphenopharyngeal, sphenoorbital, sphenomaxillary, and sphenothmoidal.

Pathology

The pathogenesis of frontal encephaloceles is not known. Currently, two schools of thought exist regarding the origin of

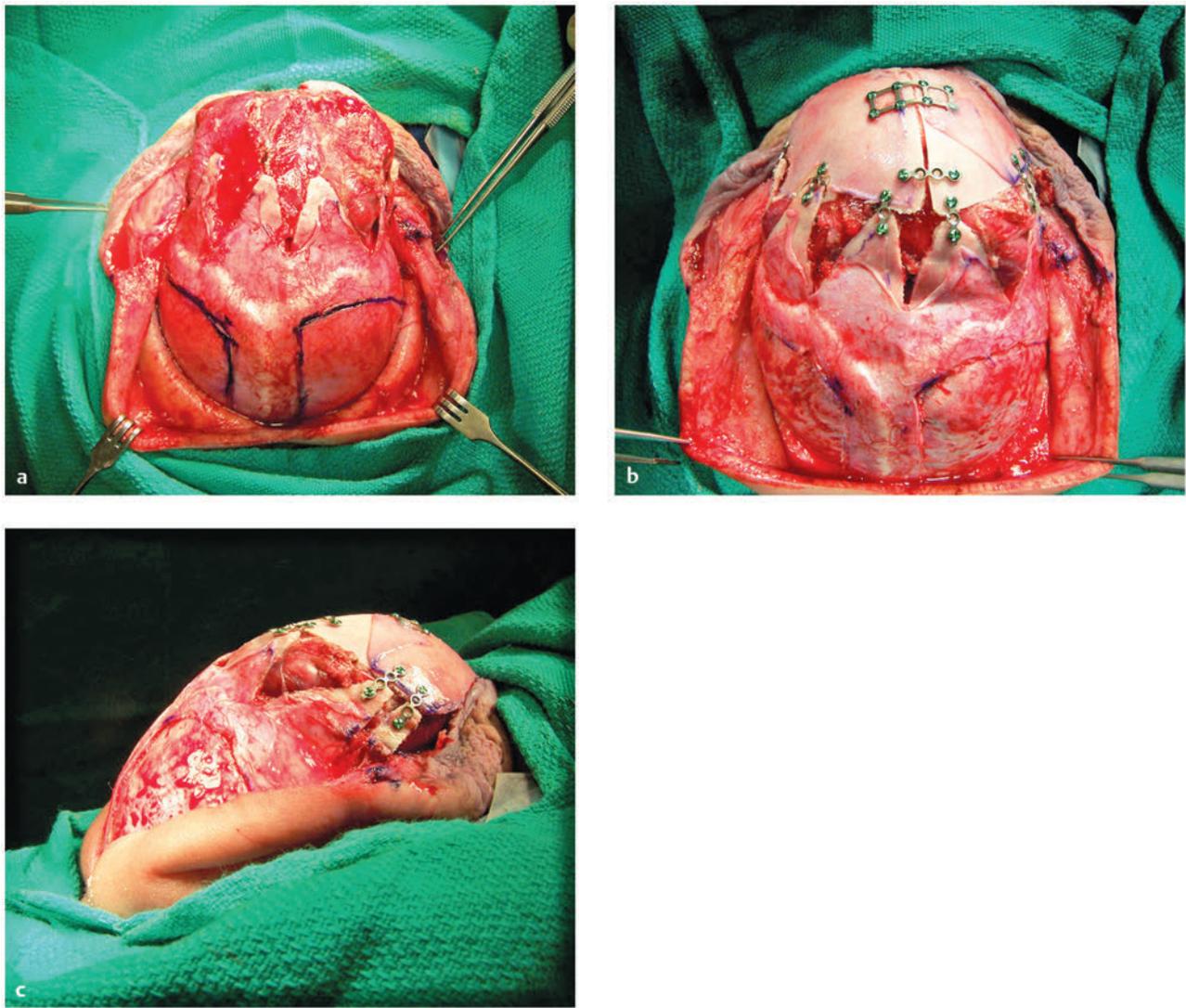


Fig. 17.15 (a) Scalp has been reflected to show the area below the lambdoid and sagittal sutures. The occipital bone was cut radially to create wedge osteotomies and accept herniated cerebral tissue. (b) Bilateral full-thickness calvarial grafts have been harvested and secured to the surrounding expanded occipital bone with titanium miniplates. (c) Lateral view demonstrates complete bony coverage of the occipital encephalocele. The donor site fully reossifies over the ensuing months.

these lesions. The first concept involves the point of weakness in the facial skeleton. The frontal bone is a membranous bone that forms from the underlying dura, whereas the ethmoid bone develops during endochondral bone formation. The function of the membranous and endochondral bone (foramen cecum is thought to result in a weak area through which the neural elements can herniate).^{43,44} A second hypothesis states that a delayed closure of the neural tube ultimately prevents normal union of the facial bones.⁴⁵ Findings of a trapped meningocele and peripheral nerve elements, as well as isolated neural tissue remnants along the original tract, appear to substantiate the second theory. However, the fact that most anterior encephaloceles are covered with normal skin indicates that

these defects are not simply a failure of neurulation. Thus, their precise etiology remains speculative. On histologic examination, the herniated tissue can vary between normal brain to fibrous atrophic nonviable tissue.⁴⁶ In the majority of cases, however, the herniating mass of a nasofrontal encephalocele consists of gliotic, nonfunctional neural tissue.^{21,31}

In contrast, occipital encephaloceles contain a much wider variety of tissue types. Simpson²⁰ reported that 32% of patients had recognizable cerebral cortex within the sac, 11% had cerebellum and fourth ventricle, and 20% had glial nodules. Oi et al⁴⁷ reported temporal lobe herniation, occipital lobe herniation, dysgenesis of the tectum, dysgenesis of the vermis, corpus callosum dysplasia, thalami fusion, brainstem kinking, and

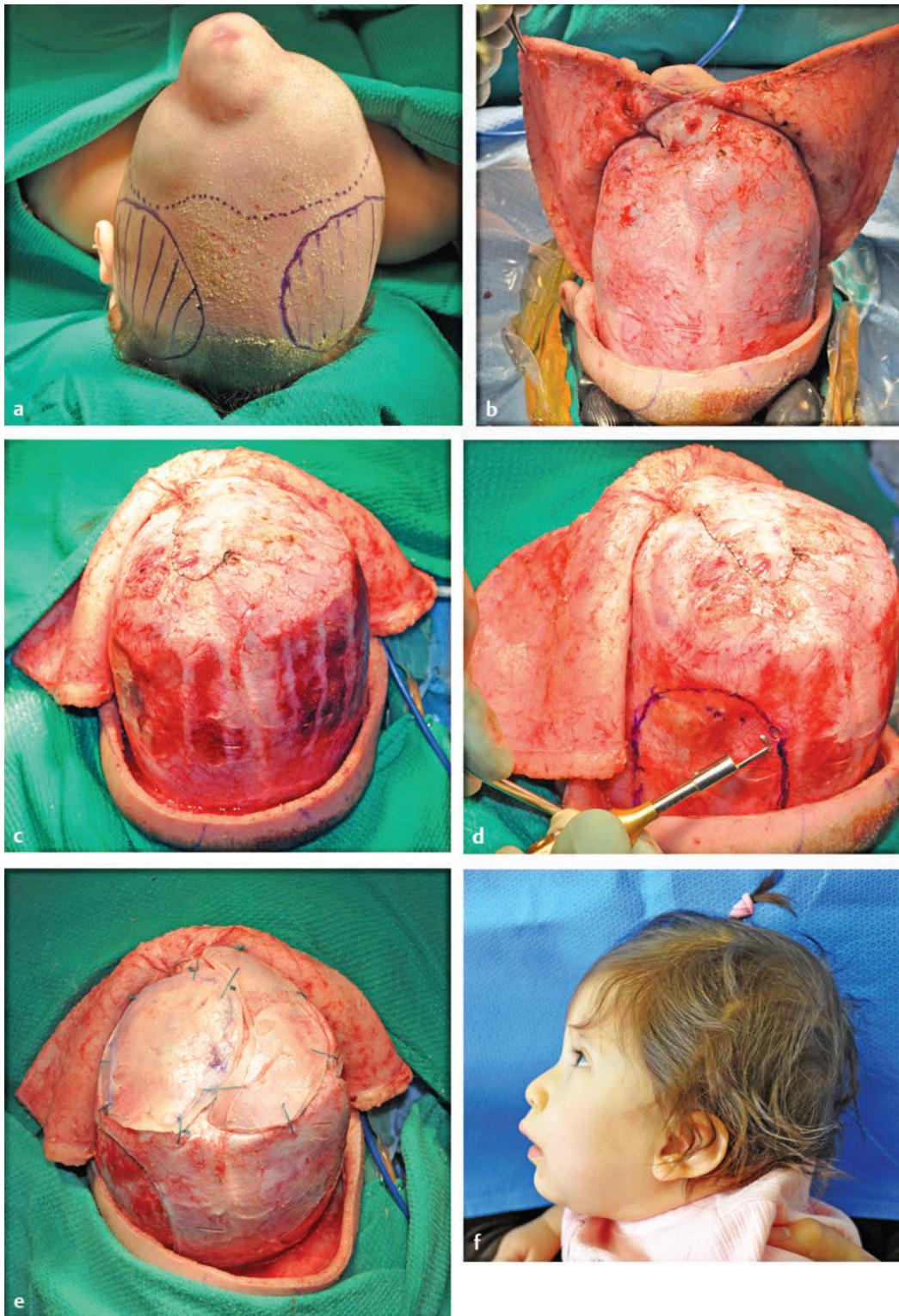


Fig. 17.16 (a) Top view of patient with a large encephalocele of the occipital area. The dotted line demarcates the edge of the bony defect surrounding the encephalocele. The rounded (solid lines) parietal areas indicate the donor site of the parietal bones. (b) A bicornal scalp incision that is a “T” toward the encephalocele is needed to provide a large area of exposure for encephalocele repair and bone harvesting and reconstruction. (c) Following complete encephalocele repair and dural closure, a large calvarial defect is noticed over the occipital area. (d) The donor site over the right parietal area is prepared. A very small bony opening is made large enough to fit the foot attachment of the drill. The solid line demarcates the osteotomy line. (e) The full-thickness calvarial grafts have been secured to the surrounding bone with nonabsorbable Ethibond (Ethicon, Somerville, NJ) sutures. (f) A lateral photograph of the patient 1 year after closure shows an excellent result with full ossification of the donor and recipient sites.

cerebellar inversion as findings associated with occipital encephaloceles. Other authors have reported the presence of supratentorial cortex with or without herniation, cerebellar tissue, and fourth ventricular tissue (see box “Associated Findings in Patients with Occipital Encephaloceles (p.211)”). Disorganized fibrous and vascular tissue was also commonly found in many patients with occipital encephaloceles.^{24,27,48}

17.1.7 Sincipital Encephaloceles

Clinical Presentation

The clinical presentation of a sincipital encephalocele can range from an occult, nondiscernible lesion to marked craniofacial deformity (see Box Signs and Symptoms of Sincipital Encephalo-

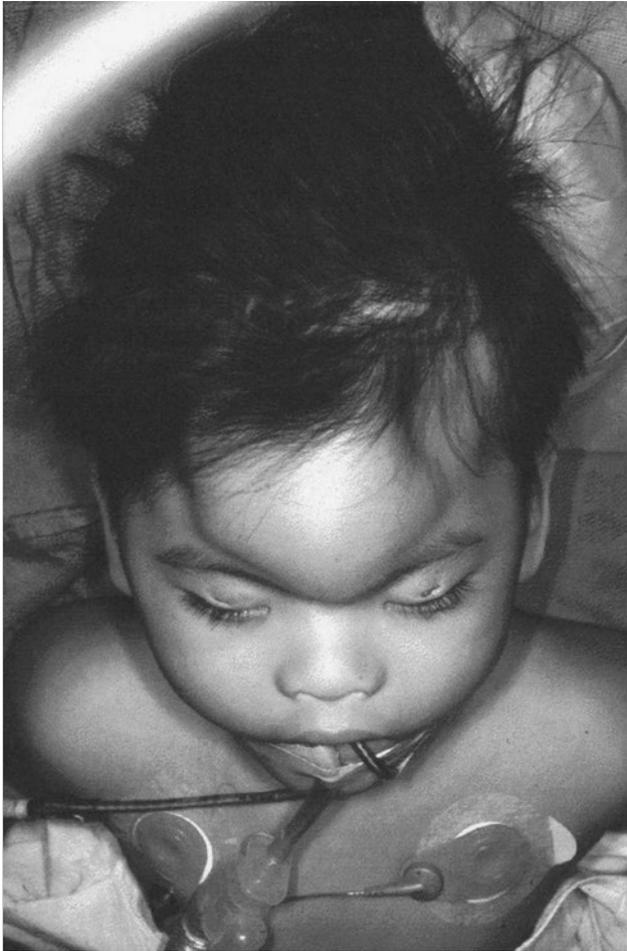


Fig. 17.17 A 2-year-old boy with a large protruding forehead mass secondary to an interfrontal encephalocele.

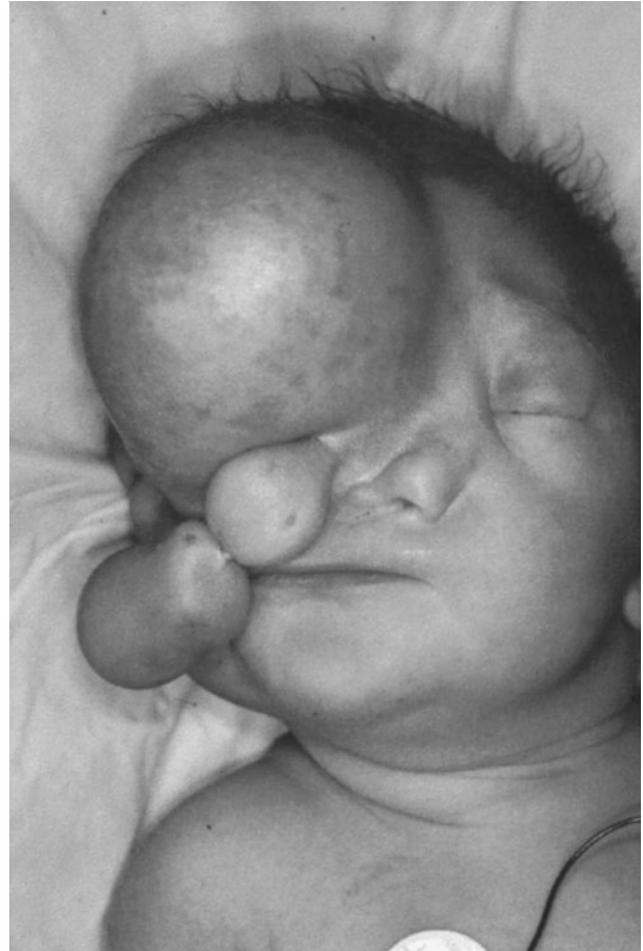


Fig. 17.18 A newborn with a complex interfrontal encephalocele. This lesion is associated with hypertelorism, nasal splaying, and a rudimentary proboscis.

loceles (p.216)). A sincipital encephalocele may vary in size from a barely noticeable mass to a lesion larger than the patient's head.

Signs and Symptoms of Sincipital Encephaloceles

- Large forehead mass
- Nasal/nasional mass
- Hypertelorism
- Telecanthus
- Orbital dystopia
- Unilateral micro-ophthalmos or anophthalmos
- Epiphora

Interfrontal Lesions

Patients present with a midline forehead mass that may be soft and pulsatile; it may be small, or it may be large, involving most of the forehead. The skull lesion is located between the nasion and the bregma, and the lesions may be simple or complex and associated with other cranial anomalies (► Fig. 17.17, ► Fig. 17.18, ► Fig. 17.19).

Nasofrontal Lesions

The herniated tissue extends through the body defect at the midline junction between the frontal and nasal bones. The mass may be seen as a small protuberance at the nasion (► Fig. 17.20) or as a larger mass extending forward and laterally to displace the nasal bones inferiorly and the medial walls laterally (► Fig. 17.21). Extension to the nasal passages can cause obstruction. (► Fig. 17.22, ► Fig. 17.23)

Nasoethmoidal Lesions

This type of encephalocele also has a cranial defect at the level of the foramen cecum; however, the herniating mass extends anteroinferiorly and passes between the nasal bones and the nasal cartilage and then extends to the surface between the structures (► Fig. 17.24). Similar to other encephaloceles, the protruding lesion may be relatively small or very large (► Fig. 17.25).

Naso-orbital Lesions

In this type of encephalocele, the mass extends inferolaterally through the frontal ethmoid junction and into the nasion and

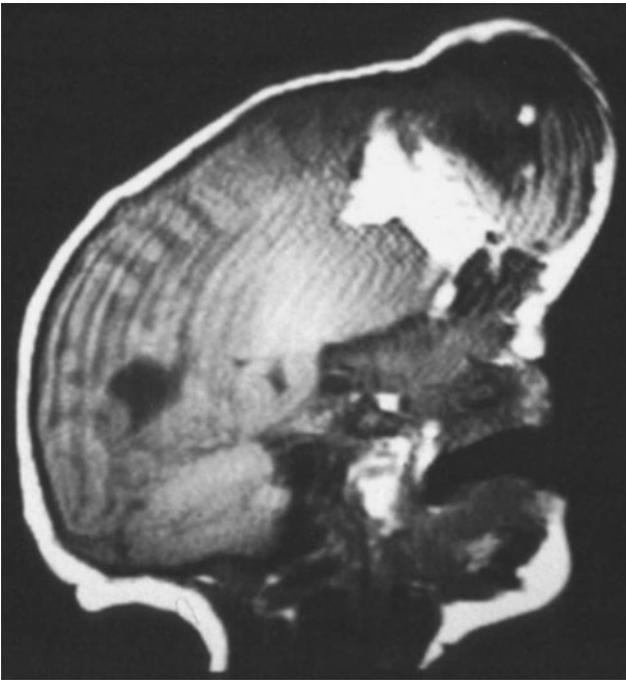


Fig. 17.19 Sagittal T1-weighted magnetic resonance image of a patient with a large interfrontal encephalocele.



Fig. 17.20 Axial contrasted computed tomographic scan of a newborn with a large interfrontal encephalocele.

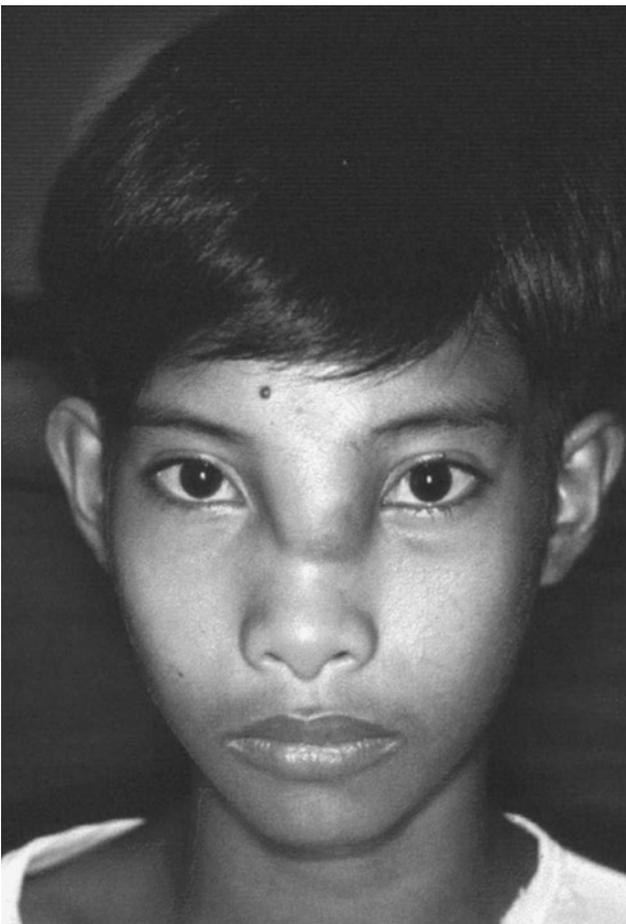


Fig. 17.21 A 12-year-old boy with a nasofrontal encephalocele. Herniating mass is localized to the region of the nasion.



Fig. 17.22 A 5-year-old girl with a large sincipital encephalocele extending into the left orbitomaxillary complex, causing marked nasal airway obstruction and ipsilateral loss of vision.

orbital areas, at the level of the middle third of the frontal process of the maxilla. These lesions cause orbital deformities: lateral displacement of the globe, upward or downward displacement of the globe (vertical dystopia) (► Fig. 17.26), telecanthus, and damage to the nasolacrimal duct leading to epiphora and dacryocystitis. Ocular deformities range from decreased global motility to hypothalamic coloboma of the

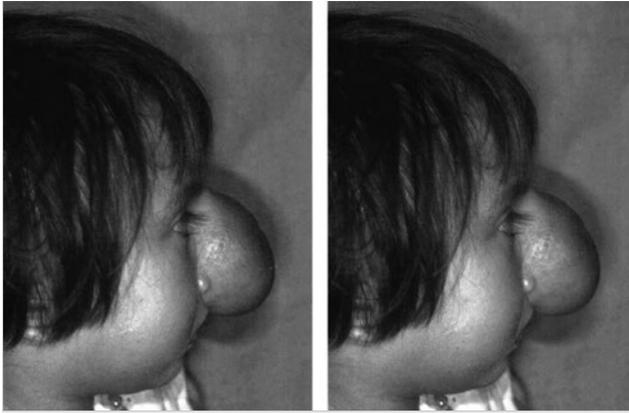


Fig. 17.23 A 7-year-old girl with a large pedunculated nasofrontal encephalocele containing a mixture of gliotic tissue and cerebrospinal fluid.



Fig. 17.25 A 3-month-old child born with a very large nasoethmoid encephalocele. The lesion, larger than the head, contained a mixture of herniated brain and cerebrospinal fluid.

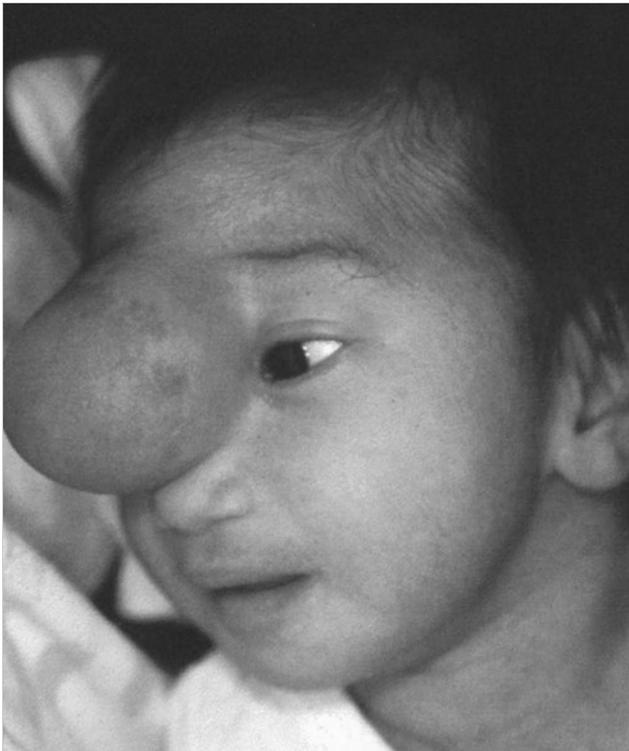


Fig. 17.24 A large nasoethmoidal lesion in a newborn child. The patient had a positive Furstenberg test (pulsation and enlargement of the mass with jugular venous compression).

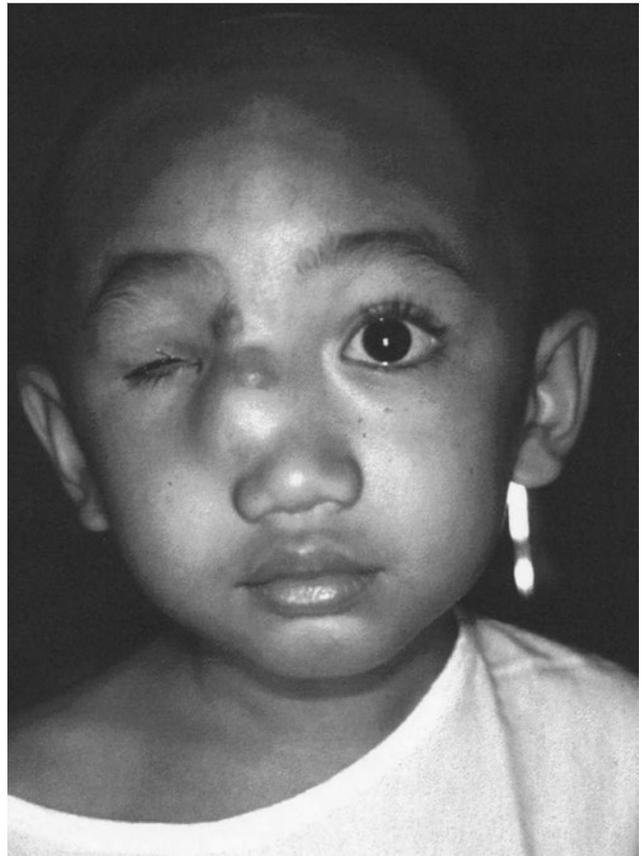


Fig. 17.26 Micro-ophthalmia and anophthalmia are ophthalmologic lesions seen in some patients with sincipital encephaloceles not associated with a syndrome. Examination of the right orbit revealed an atretic, nonfunctional globe.

optic nerve, and even anophthalmia (► Fig. 17.27).^{28,46} Basal encephaloceles do not have the obvious clinical characteristics of sincipital lesions. As previously described, these lesions are classified according to the location of the bony defect and extension of the herniated mass. Transethmoidal lesions have a bony defect at the level of the cribriform plate and extend through the ethmoid sinuses into the anterior aspect of the nasal cavity. Sphenoethmoidal lesions extend

through defects in the posterior aspect of the cribriform plate at the junction with the sphenoid bone and extend into the posterior nasal cavity; transsphenoidal encephaloceles extend into the epipharynx or the sphenoid sinus.



Fig. 17.27 A 7-year-old patient with a nasofrontal encephalocele. Note extension of the mass into the right orbit along with inferior and lateral displacement of the globe. Ocular motion was significantly restricted.

Spheno-orbital encephaloceles extend into the orbit via the superior orbital fissure and may present with proptosis and exophthalmos. In the majority of cases, these lesions present with characteristics that help differentiate encephaloceles from nasal polyps; for example, (1) encephaloceles tend to occur in children, whereas polyps are more common in adults; (2) encephaloceles are located in the midline, medial to the middle concha, whereas polyps are located lateral to the middle concha; and (3) encephaloceles are firmly attached to the medial surface of the septum, whereas polyps tend to be pedunculated and laterally located.²² A positive Furstenberg sign (visible swelling and pulsation of the mass with jugular venous compression) will indicate the presence of an encephalocele. Polyps do not swell or pulsate.

Diagnostic Studies

At the present time, CT and MR imaging are the diagnostic tests of choice, and they have supplanted all other tests. CT scans (axial, coronal, and sagittal reconstructed images) are indispensable for ascertaining the extent and location of the cranial defects (► Fig. 17.28).⁴⁹ Brain algorithms allow an accurate determination of whether CSF or gliotic tissue is present within the sac. However, triplanar MR images are the gold standard for ascertaining the extent of neural herniation. MR images are necessary for the complete visualization of basal encephaloceles, particularly those associated with the herniation of hypothalamic or diencephalic masses. MR angiography is valuable in assessing the vasculature associated with deeply located encephaloceles. Because sincipital encephaloceles are not commonly



Fig. 17.28 Axial computed tomographic scan of a patient with a sincipital encephalocele extending into the nasofrontal area.

associated with major vascular anomalies, there is no role for cerebral angiography in the diagnostic work-up of patients with these lesions.

Surgical Treatment

A variety of surgical approaches have been proposed for the surgical treatment of sincipital encephaloceles.^{50-61,63-65} These can be divided into two major categories: intracranial and extracranial. The timing of surgery also varies, but unless there is CSF leakage, sincipital encephaloceles can be treated electively. Ideally, these lesions should be treated early in infancy to prevent the deleterious secondary effects of an enlarging encephalomeningocele on craniofacial structures. The goals of the surgical treatment of sincipital and frontal encephaloceles include the following: (1) resection of the herniated mass flush with the floor of the anterior cranial fossa; (2) adequate repair of the dural defect with a pericranial patch graft; (3) prevention of postoperative CSF leakage; (4) correction of hypertelorism, if present; (5) reconstruction of the nasal elements, if necessary; (6) alignment of the horizontal ocular axis with medial cantho-pexy; and (7) cannulation of obstructed nasolacrimal ducts. Properly trained craniofacial teams can achieve all these goals with minimal morbidity and without mortality. Extension of these lesions into the facial skeleton requires the input of craniofacial surgeons to obtain the best possible results.

Although some authors have advocated two-stage procedures, the current method of choice involves a single operation. The neurosurgical team will resect the encephalocele and close the dural and cranial defects, and the plastic surgery team will proceed with craniofacial reconstruction of the defect, hypertelorism correction (if needed), nasal reconstruction, and dermal closure.

Our preferred method of treatment for these encephaloceles consists of the use of a minimally invasive craniotomy (nasional craniotomy) that is located below the bregma and involves the removal of a small rectangular piece of bone extending from the level of the eyebrows down to the tip of the nasal bone. After the area is exposed with a bicoronal scalp flap, a drill (Midas Rex C1 bit; Medtronic Neurosurgical, Goleta, CA) is used to create the osteotomies. Following removal of the bone, the dura and base of the herniating encephalocele are exposed. Transection of the gliotic brain is made along a line parallel to the cribriform plate. The herniated tissue can then be removed from the orbits, maxilla, and nasal cavities. A vascularized pericranial flap can be brought down to the empty cavities in order to obliterate dead space and seal it from the cranial cavity. A vascularized or free pericranial graft is used to close the dura along the cribriform plate area. A small piece of split calvarial graft can be used for reconstruction of the bone defect of the anterior cranial fossa. A long rectangular strip of full-thickness or split-thickness calvarial bone can be used as a cantilever graft to reconstruct the bridge of the nose. The presence of telecanthus can be corrected with the use of wire to reduce and medialize the medial canthal ligaments. Closure of the bicoronal scalp flap can be done in a standard fashion with absorbable galeal sutures and scalp staples.

Prognostic Factors and Outcomes

Advances in surgical techniques and anesthetic management currently allow the performance of major craniofacial operations without intraoperative mortality or major complications.

The majority of patients with nasofrontal encephaloceles have normal or nearly normal intelligence and ultimately do well following the repair of their congenital deformity. These operations are well tolerated by the patients if the surgical team ensures proper preoperative screening and medical preparation. Review of our experience following the treatment of 42 patients with sincipital encephaloceles reveals no intra- or postoperative mortalities. Morbidities were confined to dacryocystitis ($n=2$), superficial cellulitis ($n=1$), and CSF leak ($n=1$). Care must be taken to ascertain the patency of the nasolacrimal duct before surgical correction of the encephalocele. If the ducts are found to be blocked, cannulation of the duct system should be undertaken. If cannulation is unsuccessful, a dacryocystorhinostomy should be considered (► Fig. 17.29 and ► Fig. 17.30). Failure to achieve duct patency will place the patient at an increased risk for dacryocystitis during the postoperative period.



Fig. 17.29 Insertion of a punctum dilator into the punctum of the right nasolacrimal system in a patient with a blocked lacrimal duct and a large nasofrontal encephalocele.



Fig. 17.30 Following dilation of the punctum, a Jones silicone lacrimal tube is inserted into the duct for expansion and dilation. The tube is left in place for up to 8 weeks.



Fig. 17.31 Aerial view of a bicoronal scalp flap demonstrates improper location of a craniotomy. Demarcated area shows a unilateral location of the craniotomy. The high location of the bony opening did not allow the surgeon adequate access to the midline nasoethmoidal encephalocele.

Published mortality rates of patients operated on for frontal encephaloceles vary between 7 and 20%.^{20,62} These reports, however, are older and do not represent the current low mortality rate (< 1%) achieved at most craniofacial centers.

Management Pitfalls

Difficulties may arise in the management of these patients in North America because of the very infrequent presentation of sincipital encephaloceles (1 in 35,000 live births). As such, the average neurosurgeon or plastic surgeon may see only one or two patients with sincipital encephaloceles in a professional lifetime. Therefore, we believe these patients should be referred to craniofacial centers with experience in treating the complex lesions. Having surgically managed several patients referred after improper resection of these masses, we have identified several potential pitfalls in their management.

Inadequate Exposure

Improper placement of the bone flap may lead to the inability to completely resect the encephalocele. A unilaterally highly placed craniotomy (► Fig. 17.31) will not allow proper access to the lesion. Although a properly placed unilateral craniotomy may give access to the lesion, a bifrontal approach is preferable. Difficulty in properly exposing the lesion may arise when a bifrontal craniotomy is placed too high above the supraorbital rims.

Inadequate Resection

An improperly approached encephalocele may not be fully resectable. If this occurs, the patient will continue to show a facial mass, which is a poor postoperative result (► Fig. 17.32 and ► Fig. 17.33).

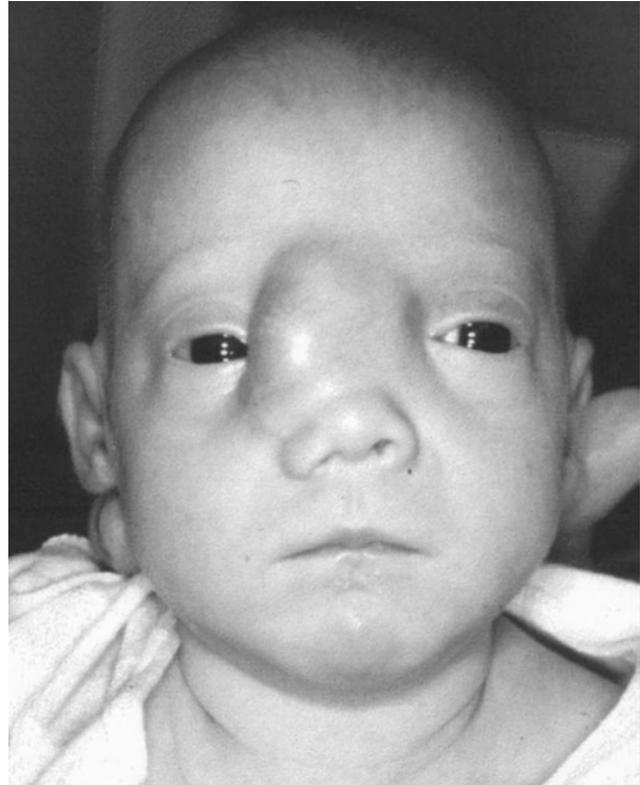


Fig. 17.32 A 1-month-old premature girl whose original repair resulted in residual encephalocele and the postoperative development of a pseudomeningocele. Note the inferior displacement of the nasal ala secondary to fluid buildup.

Improper Closure

This can lead to postoperative CSF leaks or pseudomeningocele formation. The use of spinal drains and/or fibrin glue significantly reduces the risk.

Insufficient Preoperative Preparation

All patients should be fully evaluated by the craniofacial team; extensive medical (pediatric), ophthalmologic, dental, neurologic, and radiologic evaluations should be performed. Failure to identify hydrocephalus will lead to postoperative CSF leaks and wound dehiscence and/or infections. All medical abnormalities (anemia, infections, malnutrition, others) should be corrected before surgical treatment. In developing countries, care should be taken to eliminate any parasitic infection that may be present preoperatively.

17.1.8 Basal Encephaloceles

Basal encephaloceles (transsphenoidal, sphenoethmoidal, transtethmoidal, and spheno-orbital) are uncommon in Western countries, making up approximately 5% of all encephaloceles. These lesions are located in the anterior skull base and may extend through bony defects in the ethmoid bone, ethmoid-sphenoid junction, or sphenoid bone. The encephalocele mass may

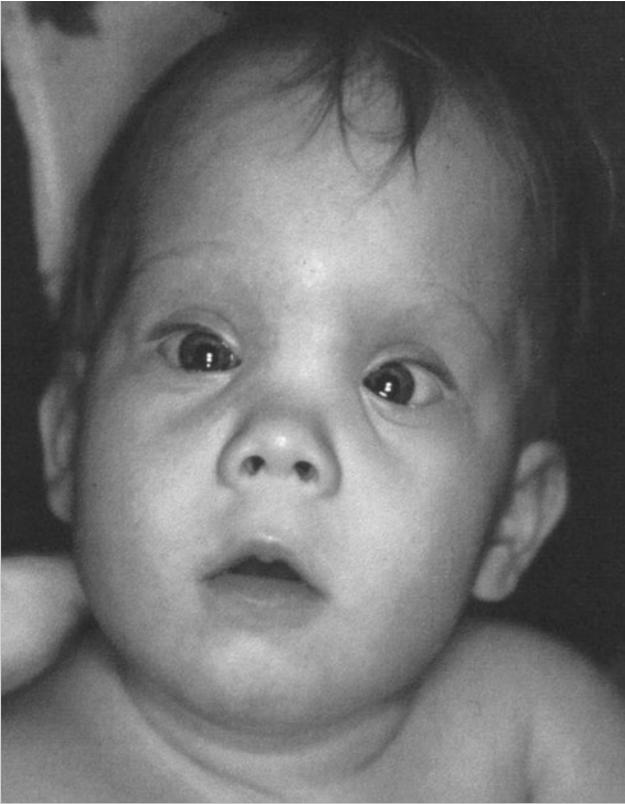


Fig. 17.33 Following correction of a postoperative pseudomeningocele with a nasional craniotomy, the patient demonstrates proper nasal and ocular alignment.

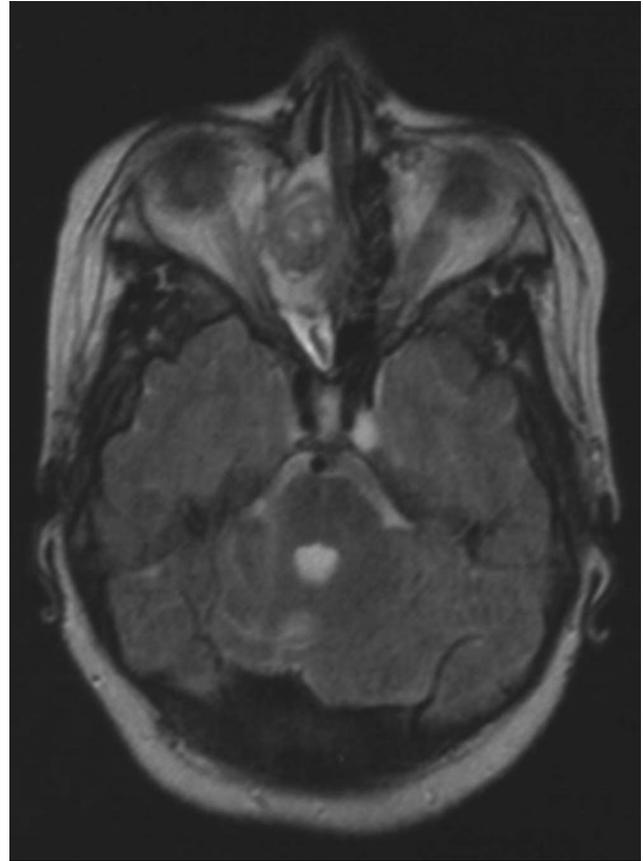


Fig. 17.35 T2-weighted axial magnetic resonance image demonstrates a basal encephalocele extending into the right ethmoid sinus and the right orbit, causing diplopia and decreased ipsilateral vision.



Fig. 17.34 T1-weighted midsagittal magnetic resonance image of a patient with a basal encephalocele extending into the sphenoid-ethmoid sinuses and upper nasal airway. The patient presented clinically with recurrent rhinorrhea and headaches.

extend into the ethmoid sinus and into the nasal cavity or through the sphenothmoid junction or sphenoid sinus into the epipharynx. The clinical presentation is such that the patient is often brought to an otolaryngologist because of a nasal or epipharyngeal mass associated with noisy, difficult breathing; recurrent upper respiratory infections; nasal discharge; recurrent meningitis; and occasional CSF leaks (especially after a “nasal polyp” biopsy) (► Fig. 17.34, ► Fig. 17.35). Clinical examination most often reveals a mass covered with mucosa in the nasal or epipharyngeal cavities, usually located in the midline and associated with a positive Furstenberg sign. Spheno-orbital encephaloceles present with progressive pulsating exophthalmos and a defect on the sphenoid bone leading to intraorbital herniation. This type of encephalocele may also reach the orbit via the superior orbital fissure. Associated ocular abnormalities include progressive visual loss, micro-ophthalmos, coloboma, hydrophthalmos, anophthalmos, and microcornia.¹¹

Treatment

The goal of treatment is to obtain a watertight dural closure of the defect following amputation of the mass or its relocation into the cranial cavity. These lesions are much more difficult to treat, given the propensity of vital structures (hypothalamus, anterior cerebral arteries, optic nerves, optic chiasm, third ventricle) to herniate. Extracranial approaches

are associated with many problems, including incomplete resection and postoperative CSF leaks. The intracranial approach is the preferred method of treatment. If the stalk is narrow, intradural exploration will allow proper amputation of the lesion and adequate dural repair with autologous pericranium. If the neck of the lesion is wide and normal structures are suspected to be herniated, every attempt should be made to relocate the vital structures into the cranial cavity. When a lesion is located in the ethmoid or planum sphenoidale, a bifrontal craniotomy will afford excellent access to the encephalocele. Additional extension laterally (pterional craniotomy) or temporally (subtemporal craniotomy) may be desired for lesions extending into the orbit or the infratemporal fossa. Following adequate amputation and dural closure, often the extracranially herniated tissue is not resected but rather allowed to shrink without the necessity for a second operation. The prognosis of patients with basal encephaloceles is usually excellent except for those in whom vital structures have massively herniated. The prognosis is better than that for occipital or parietal encephaloceles. As with other types of encephaloceles, proper preoperative evaluation, planning, and surgical corrective procedures are essential for obtaining a successful outcome, including use of endoscopic technique.⁶⁷

17.1.9 Cranial Vault Encephaloceles

In addition to nasofrontal and occipital areas, encephaloceles may also arise from the parietal and temporal bones. Parietal encephaloceles are relatively uncommon, although in some series the incidence has varied between 12.5⁶⁹ and 37.5%.⁷⁰ McLaurin⁷¹ presented 13 patients with intraparietal encephaloceles. Four of them had agenesis of the corpus callosum, three had communication of the lateral ventricles with a surface lesion, and two had Dandy-Walker cysts. He reported a highly unfavorable prognosis in these patients with parietal encephaloceles. Simpson⁹ reported 13 patients with parietal encephaloceles, four of which were associated with agenesis of the corpus callosum or holoprosencephaly. Yokota et al⁷⁰ reported 15 patients with parietal encephaloceles and also found that they carried a much less favorable prognosis than those in the occipital region, regardless of the type. This poor outcome was related to the accompanying cerebral malformations, which appeared to be more frequent and severe than those associated with encephaloceles in the occipital or frontal area. Associated anomalies with parietal encephaloceles in this series included massive cerebral herniation, Chiari 2 malformations, diencephalic cyst, vermis agenesis, corpus callosum agenesis, and midline porencephaly.

17.1.10 Temporal Encephaloceles

Encephaloceles can also occur in any area of the temporal bone. The true incidence of temporal encephaloceles is unknown. Wilkins et al⁷² categorized this type of encephalocele into five subtypes. Lateral temporal encephaloceles extend through a defect at the pterion or asterion. This lesion is apparent during early infancy and most commonly found in females. Anterior temporal encephaloceles present with a defect in the wing of the sphenoid, with herniation into the posterior orbital area

and unilateral pulsating exophthalmos. Anterior medial encephaloceles extend through a defect of the anterior wall of the middle fossa and into the sphenoid sinus. Patients may present with CSF rhinorrhea, or the lesions may be detected incidentally. Posterior temporal encephaloceles (aural) herniate through the tegmen tympani into the tympanic antrum or epitympanic recess. Patients present with CSF in the middle ear, rhinorrhea or otorrhea, decreased hearing, and occasional meningitis. Anterior-inferior temporal encephaloceles project through the anterior floor into the infratemporal fossa. Patients most commonly present with simple or complex partial seizures.⁷² Endaural encephaloceles of the middle fossa may be repaired from below (mastoidectomy) or from above (middle fossa craniectomy) or a combination of these.⁷³ Larger encephaloceles should be approached via craniotomy. When the encephalocele impinges on the ossicular chain, a combined tympanomastoid-middle fossa craniotomy approach is the procedure of choice.⁷⁴

A combination of brain MR imaging and CT can be used to provide the treating surgeon with the necessary anatomical knowledge to resect and reconstruct the encephalocele. Anterior or medial temporal encephaloceles can be approached with a standard pterional craniotomy. Posteriorly located lesions can be treated with a subtemporal craniotomy. As with other encephalocele types, the herniating brain should be amputated and resected.⁶⁸ The cranial defect is repaired with a customized split-thickness calvarial graft obtained from the approach craniotomy (► Fig. 17.36, ► Fig. 17.37). The dura can be repaired with a free pericranial graft. This surgical approach can lead to definitive and long-lasting correction of the condition with excellent results and minimal morbidity or complications.

17.2 Meningocele

Meningocele are lesions in which an underlying skull defect is associated with herniation of the leptomeninges and CSF.

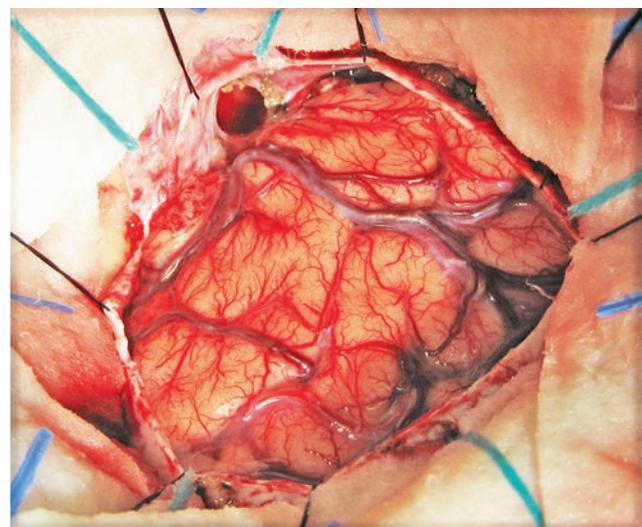


Fig. 17.36 Temporal fossa encephalocele. Craniotomy demonstrates a round bone defect on the floor of the middle fossa, through which a part of the inferior temporal lobe has herniated.

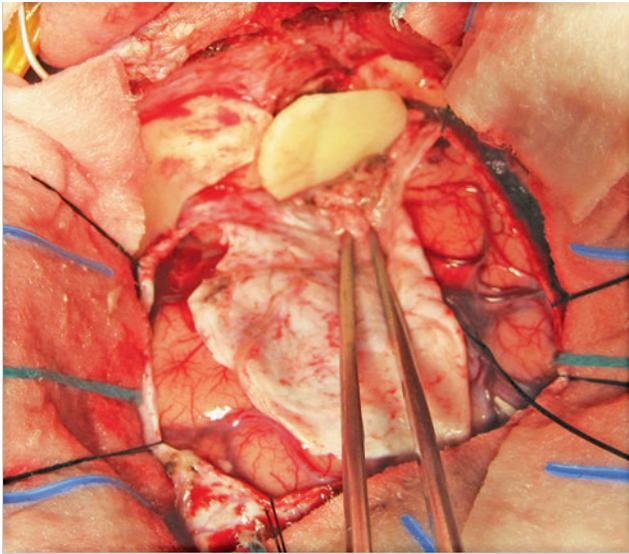


Fig. 17.37 After resection of the encephalocele, the temporal bone is reconstructed with a split-thickness calvarial graft. A vascularized pericranial graft is then used to further seal the defect.



Fig. 17.39 A 7-month-old child presented with an enlarging pulsatile mass over the area of the anterior fontanel. Surgical exploration revealed a simple meningocele without sinus involvement.

No neural tissue is found in these lesions (► Fig. 17.38). They are located anywhere that encephaloceles are encountered (► Fig. 17.39). Primary meningoceles are congenital in nature and typically present at an early age. Secondary meningoceles

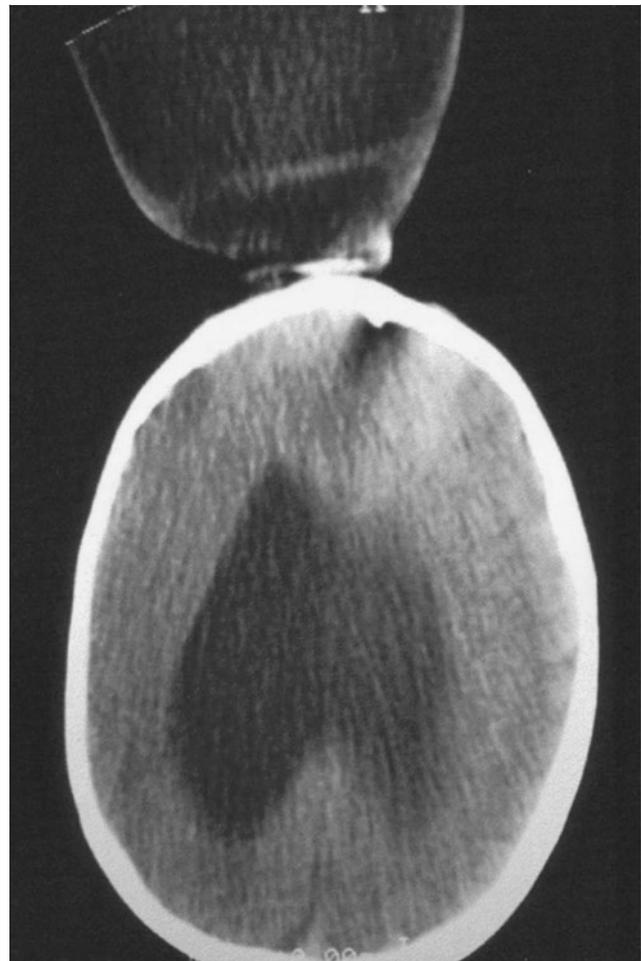


Fig. 17.38 A very large frontal meningocele in a 5-month-old child. No neural elements were found inside the sac. The patient required a shunt after closure of the meningocele.

are commonly due to postsurgical defects. They occur whenever a bone flap is removed and the dura is left open (as in decompressive craniectomies for malignant brain swelling) (► Fig. 17.40). The treatment includes closure of the dural layer, either primarily or with a dural substitute, in a watertight fashion. The skull defect is then closed with an autologous acrylic or hydroxyapatite cranioplasty. These lesions have a much better prognosis than encephaloceles.

17.3 Cranial Dermal Sinuses

Congenital cranial dermal sinuses are midline tracts lined by stratified squamous epithelium that extend between the superficial dermal layers and deeper cranial structures (see box “Signs and Symptoms of Cranial Dermal Sinus Tracts (p.225)”⁷⁵). The depth of extension is variable and may include central nervous system structures and their coverings. Given its internal architecture, the tract may expand anywhere along its length (particularly at either terminus) to form dermoid or, less commonly, epidermoid cysts. Although dermal sinuses can occur anywhere along the neural axis, in the cranial vault the majority (85%) are located in the occipital region near the inion,

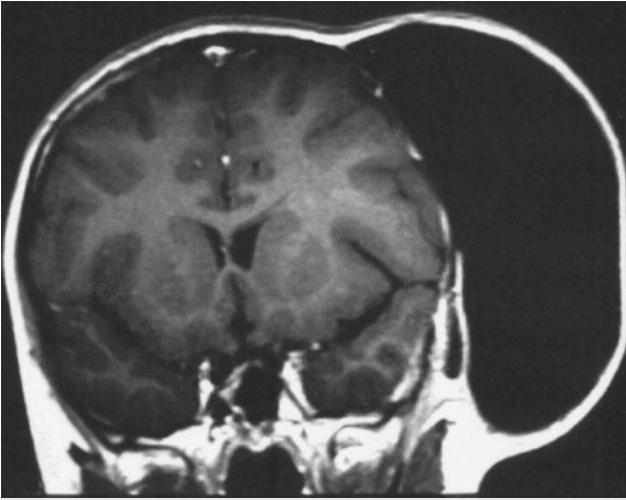


Fig. 17.40 T1-weighted coronal magnetic resonance image of a 12-year-old boy who underwent a craniotomy for evacuation of a subdural empyema. The bone flap was left out, and the dura opened as a result of massive brain swelling. This acquired meningocele contained 510 mL of cerebrospinal fluid and subsided with replacement of the bone flap.

11% in the frontal region (nasion and nasal structures),^{11,76,77} and 5% in the posterior parietal area. Eighty-nine percent of dermal sinuses are associated with inclusion tumors; dermoid cysts are the most common type. Eighty-two percent are found to extend subdurally or deeper, and 18% are found to be purely extradural.⁷⁸

Signs and Symptoms of Cranial Dermal Sinus Tracts

- Midline facial or occipital dimple
- Nasal mass
- Long, fine, black hairs and a dimple
- Recurrent meningitis
- Drainage from the dermal pit

17.3.1 Pathology

Nasal dermal sinus tracts result from an alteration of the embryologic development of the nasofrontal region. To better understand the genesis of these lesions, we present a brief review of the normal sequence of events. Concurrently with closure of the anterior neuropore at approximately 24 days of gestation, mesodermal tissues begin to develop into bone, cartilage, vessels, and meninges. At approximately 50 days of gestation, the nasal and frontal bones develop by intramembranous ossification of the mesoderm.⁷⁹ At these early stages, the nasal and frontal bones remain separated by a space called the fronticus nasofrontalis. The floor of the skull base develops by endochondral bone formation. The nasal capsule, part of the chondrocranium, is a cartilaginous mass that will give rise to the lateral masses of the ethmoid inferior concha and the anterior two-thirds of the midline nasal septum, which remains cartilaginous.

The prenasal space develops between the nasofrontal bones and the nasal capsule. At the end of the second gestational month, a diverticulum of dura extends anteroinferiorly through the prenasal space transiently to reach the superficial ectoderm that will become the skin of the nose. As growth progresses, the nasal process of the frontal bone grows inferiorly to surround dural projections, creating a canal known as the foramen cecum. The foramen cecum eventually fuses with the fronticus nasofrontalis at the area of the future cribriform plates. The dural diverticulum eventually involutes and retracts through the foramen cecum. The most widely accepted theory of nasal sinus tract development implicates a defective or incomplete process of nasofrontal fusion. If the dural projection remains adherent to the skin, a small dimple may be seen at the external orifice of the sinus tract. The sinus can terminate anywhere along the path of the dural projection or even extend through the foramen cecum into the cranium.⁸⁰ Dermoid cysts or tumors can develop as a result of cellular desquamation of the dermal elements lining the tract. Upon histologic examination, the dermoid sinus contains both ectodermal and mesodermal derivatives. It is composed of a stratified squamous epithelial lining with specialized adnexal tissues that may include hair follicles, pilosebaceous glands, and smooth muscle.⁸¹ Intracranial extension of the dermal sinus tracts is most frequently extra-axial, usually attached to the dura or confined within the leaves of the anterior falx. Intra-axial extension into brain parenchyma is less common.

17.3.2 Signs and Symptoms

Cranial dermal sinuses can present at any age, although the majority (84%) are diagnosed in patients younger than 5 years of age. Males and females are affected equally.⁸² There may be no symptoms, or the clinical presentation may include recurrent episodes of meningitis, mass lesions, skin dimples, or a combination thereof.^{80–82} The mass lesions may be superficially located (subcutaneous) or deep-seated (intracranial). Nasal dermal sinus tracts may present as a visible cutaneous opening or dimple and/or an associated nasal mass. Although the lesions are most commonly located along the midline, paramedian locations have been reported. The dermal sinus pit may be anywhere between the nasal columella and the nasion.⁸³ Dermoids at the nasal tip are not uncommon (► Fig. 17.41). Up to one-third of patients can be asymptomatic at the time of diagnosis. Local drainage of uninfected sebaceous debris may be seen, and some patients will present with an infected, swollen, erythematous, and tender tract.⁸⁴ Fine black hairs arising from a midline nasal dimple should alert the clinician to the strong possibility of an underlying sinus tract. Infection of an intracranial or extracranial site or both was found in 43% of all patients in one series, and 51% had an associated mass lesion.¹¹ Patients should be suspected of harboring a dermal sinus tract when they present with recurrent bouts of meningitis of unknown etiology. *Staphylococcus aureus* is the most common cause of recurrent meningitis in these patients.⁸⁴ A careful examination of the entire midline structure should be undertaken, including shaving the hair over the inion. Occipital dermal sinuses commonly present with a dermal pit near the inion, although the dimple may be located over the supratentorial area or as far inferiorly as the upper cervical spine.⁸⁵ Hemangiomatous skin discolorations commonly surround occipital dermal tracts. Occasionally, the

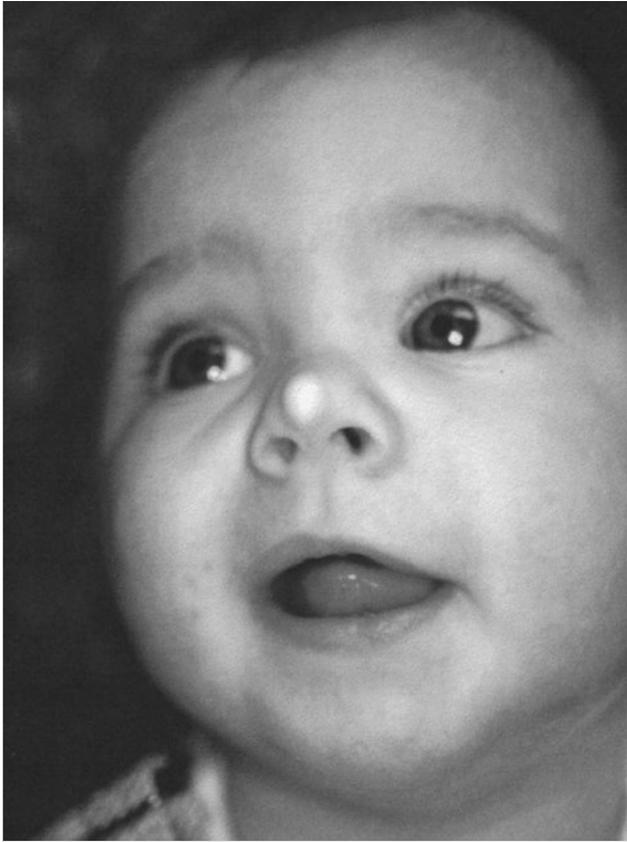


Fig. 17.41 A 7-month-old boy born with a small dimple at the tip of his nose. An enlarging mass began to grow at 4 months of age. The lesion represents a nasal dermoid.

only sign may be a small amount of discharge from an occult dermal pit within the hairline and recurrent bouts of meningitis (► Fig. 17.42).

17.3.3 Diagnostic Studies

Currently, the best method for diagnosing dermal sinus tracts includes a combination of MR imaging and CT.^{86–88} MR imaging, with and without gadolinium, may demonstrate soft tissue intensity in the subcutaneous fat of the nose, representing the tract itself (► Fig. 17.43). Associated dermoid tumors can be visualized and exhibit short T1 and T2 relaxation times. Epidermoids show prolonged T1 and T2 relaxation times compared with brain tissue. CT (bone algorithm) can demonstrate the tract traversing the bony skeleton (► Fig. 17.44). The most important information obtained from these studies is an assessment of the extent of the dermal sinus, and particularly a determination of whether intracranial extension of the sinus or an intracranial cyst is present (► Fig. 17.45). It must be realized, however, that both of these imaging modalities may have pitfalls. The fatty metamorphosis of the marrow and the signal intensities that accompany frontal sinus aeration can misrepresent the findings. These changes occur between 1 and 5 years of age, the same age range at which most patients are most likely to present. Care must be taken not to confuse the crista galli or the subadjacent plate of the ethmoid for a dermoid tumor. The

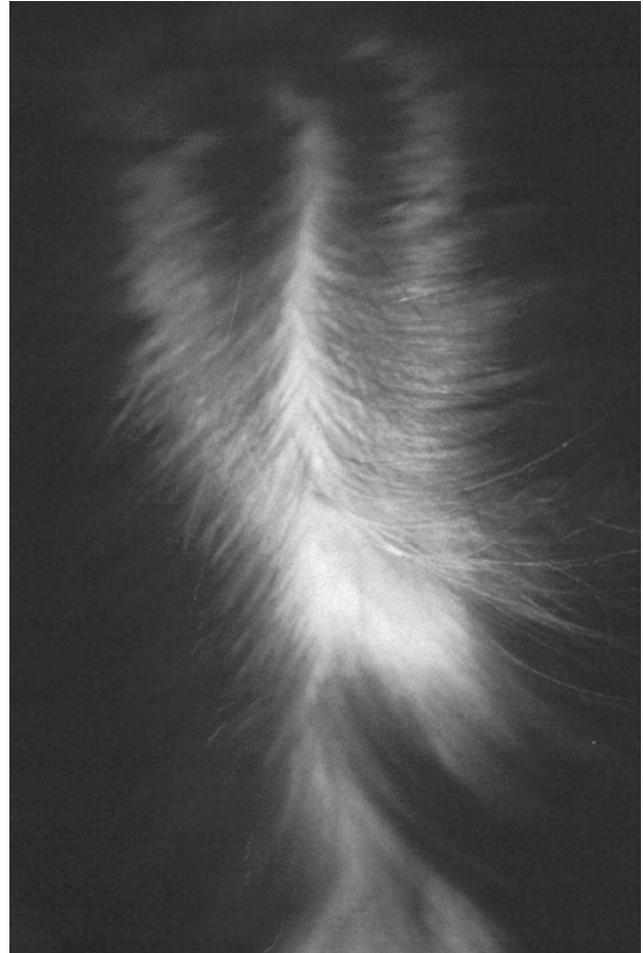


Fig. 17.42 An occipital dermal sinus tract in a 14-year-old girl. A small amount of purulent noninfected material is seen at the base of the lesion. Other findings include a small area of alopecia and heman-giomatous skin discoloration.

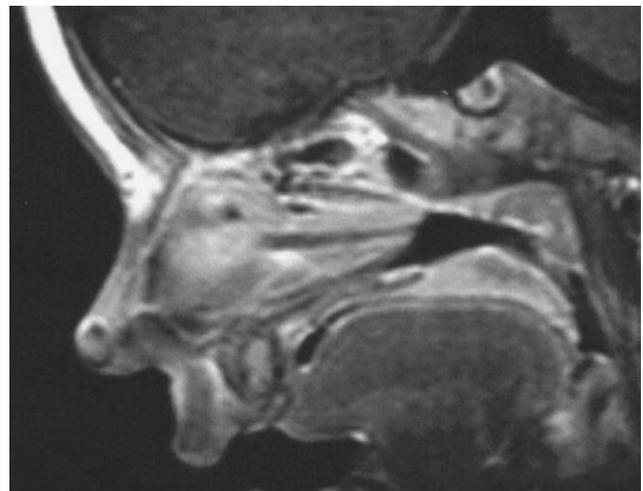


Fig. 17.43 T1-weighted sagittal magnetic resonance image with contrast demonstrates an enhancing round mass at the tip of the nose and an enhancing dermal sinus tract extending intracranially.

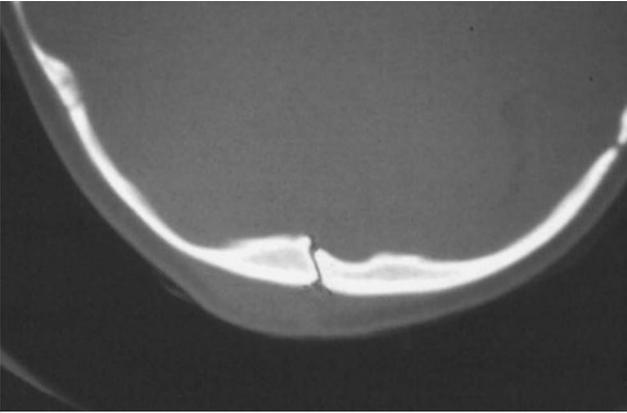


Fig. 17.44 A computed tomographic scan (bone algorithm) immediately below the inion demonstrating a small tract extending through the outer and inner tables of the skull.

central portion of these bones begins to undergo fatty changes at approximately 12 months of age. Such misinterpretation may lead to an unnecessary craniotomy. Plain skull films do not yield significant information and are not currently used.

17.3.4 Surgical Treatment

The surgical principle governing the management of any dermal sinus (cranial or spine) is that the tract and any associated dermoid tumors must be prophylactically removed following diagnosis. Furthermore, excision of the tract should include its full extradural and intradural extensions. The goal is to remove these lesions before they become infected or meningitis develops. Simple excision of the sinus tract to the level of the bone is inadequate. Because these tracts are lined with epithelium that can lead to tumor development, an incomplete resection may lead to subsequent meningitic episodes or deep tumor development. If the excision of these lesions is delayed until they become symptomatic (infected), the subsequent management will be more difficult, creating a less than optimal final result. If the patient presents with an infected tract, meningitis, or hydrocephalus, these conditions need to be treated and controlled before surgical resection.

When nasal lesions are treated, a plastic surgeon should be part of the team. Our approach is to perform a single-stage procedure, although some authors advocate staged operations whereby a craniotomy is done first and the nasal component is resected at a later date.⁸⁹ We see no advantage in taking such an approach. Given that nasal tracts originate in the nose and extend through the foramen cecum, a midline partial rhinotomy and a frontal craniotomy may be needed to resect these lesions fully. Intracranial dermoids are removed, the dura closed, and the tract amputated below the level of the bone. The entire tract should be fully removed from the skin and intranasal structures to prevent future recurrence or infection.⁷⁹

17.3.5 Prognosis

Patients with completely resected asymptomatic tracts and dermoid tumors have an excellent prognosis. Incompletely resected tracts place the patient at higher risk for the development of

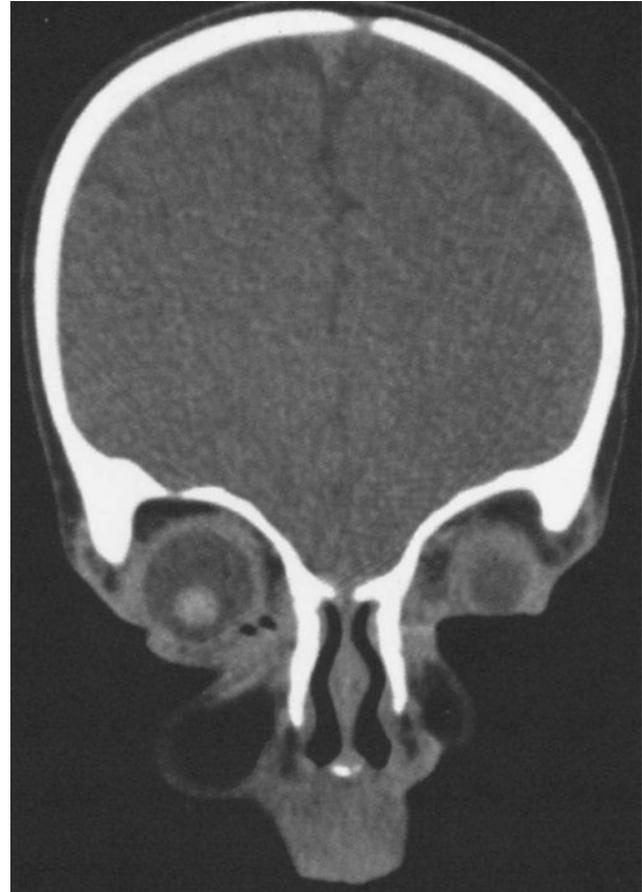


Fig. 17.45 A computed tomographic scan, coronal view, showing the bony canal of a dermal sinus tract anterior to the crista galli and cribriform plate.

meningitis, tract infection, and cystic tumors. Every attempt should be made to achieve gross total resection of these lesions.

Pearls

- If there is evidence of nasolacrimal duct obstruction in a patient with a sincipital encephalocele, the duct should be cannulated with a Silastic tube (Dow Corning, Midland, MI). The tube should be left in place for 6 months to prevent dacryocystitis and reestablish duct patency.
- Patients who have sincipital encephalocele with ventriculomegaly should undergo ventriculoperitoneal shunt placement before encephalocele repair to prevent postoperative CSF leaks.
- Every attempt should be made to preserve “normally functional” brain and occipital encephaloceles. However, most often the tissue is fibrous, gliotic, and nonfunctional and so can be easily amputated.
- Dermal sinus tracts should be excised “prophylactically,” and the tract and associated dermoids should be totally excised to prevent recurrence.
- The use of full-thickness calvarial grafts in young infants provides an excellent method for obtaining complete osseous closure of the bony defects associated with cranial encephaloceles.

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18 Congenital Lesions of the Scalp and Skull

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Congenital lesions of the skull and scalp are common, and the vast majority of them are benign. Nevertheless, the treatment of these lesions requires a good understanding of their natural history, radiographic findings, diagnostic criteria, and treatment options. Treatment ranges from observation to multidisciplinary care involving multiple specialists. Although we cannot cover all the lesions, we attempt to discuss some of them that are seen commonly in a pediatric neurosurgical practice. In particular, we discuss three commonly encountered entities: aplasia cutis congenita, atretic cephaloceles, and parietal foramina/cranium bifidum.

18.1 Aplasia Cutis Congenita

18.1.1 Background

Aplasia cutis congenita (ACC), also referred to as cutis aplasia, is a heterogeneous condition in which one or more components of the scalp and/or skull are absent at birth. Histologically, cutis aplasia is characterized by a lack of epidermis, dermis, fat, and in severe cases muscle and/or bone (► Fig. 18.1). Although the condition was first described in the extremities by Cordon in 1767,¹ and any part of the body can be affected, 85% of cases involve the scalp.²⁻⁷ ACC of the scalp was first described in 1826 by Campbell,⁸ and Billard later reported a concurrent cranial defect.^{3,8-10} Since that time, there have been hundreds of reports of this condition.³

ACC is reported to occur in about 1 in every 10,000 live births and is more common in females than in males.^{2,11} Nevertheless, ACC is likely underreported because mild cases may be confused with other scalp conditions.² The cranium and dura are affected in about 15% to 30% of cases² (references 5, 6, 8, and 9 in Bharti et al²), and these cases require acute treatment. Dessiccation of the dura, especially over the superior sagittal sinus, can result in significant morbidity or death.



Fig. 18.1 Aplasia cutis congenita in a newborn with full-thickness defect and exposed dura.

18.1.2 Causes

A number of theories have been posited over the years to explain the cause of this condition. The etiology seems to be multifactorial, as no single theory seems to explain ACC fully. As with many conditions, both genetic and environmental factors appear to be related to ACC. Most cases of ACC occur sporadically, but there is a family history in 40% of affected children. The majority of hereditary cases of ACC are passed in an autosomal-dominant fashion,¹²⁻¹⁶ although autosomal-recessive inheritance has also been reported^{13,14,17,18}

Multiple syndromes show association with ACC. One of the best known is Adams-Oliver syndrome. Children with Adams-Oliver syndrome can have ACC, with or without involvement of the skull or dura. In addition, these children may have shortened or absent fingers or toes, loss of the metacarpals, absence of the lower extremities below the calf, and mottling of the skin. Adams-Oliver syndrome is thought to be inherited in an autosomal-dominant pattern.^{2,13,19,20} Other syndromes associated with ACC include Setleis syndrome, Anderson-Hollister-Szalay syndrome, Johanson-Blizzard syndrome, and Goltz syndrome.^{2,5,21,22}

A number of environmental factors have also been cited as possible causes of ACC. According to one theory, amniotic adhesions to the skin of the fetus tear off, leaving areas devoid of skin. This theory seemed to have been disproven, at least in most cases, because most examined cases showed normal placentas.^{3,23}

Teratogens have also been implicated in causing ACC. These include heroin, alcohol, cocaine, methotrexate, antithyroid medications, angiotensin-converting enzyme (ACE) inhibitors, and other medications.^{2,5,6,24} Another possible mechanism is tension on the fetal skin during development. It is thought that tension on the vertex, which sustains the greatest amount of stretch during head growth, can disrupt the skin, leading to ACC.^{2,5,24,25} Other factors that have been proposed as possible mechanisms leading to ACC include vascular disruption of the fetus leading to ischemic injury^{2,4,6,22,24,25}, intrauterine infection, and intrauterine trauma.^{2,6,26} Of note, Ingalls in 1933 found that there was an associated fetus papyraceus, or mummified dead fetus, at the delivery of many newborns with ACC of the trunk or limbs.^{3,27}

As one can see from this myriad of possible causes, there is no unifying theory to explain ACC. Rather, it is thought to be multifactorial in etiology, with both genetic and environmental causes. Different classification schemes have been proposed to describe the disease. Frieden devised a nine-part classification system based on area of the body affected, other abnormalities, and inheritance pattern.³

18.1.3 Pathology

Lesions of ACC do not have the normal histology of stratified squamous epithelium of the scalp. Instead, they show a loose fibrous stroma devoid of hair follicles, epithelium, and sweat glands. They are covered by a thin epithelial membrane with a thickness of one cell layer.^{13,28-30}

18.1.4 Clinical Presentation

The presentation of ACC can vary greatly, and the management of a lesion requires a careful examination and understanding of its extent. More than 80% of lesions are located at or near the midline, and many are situated close to the parietal hair whorl.^{3,13,28,31} These lesions can present in all sizes. Most are less than 2.5 cm in diameter, but some can be more than 8 cm in diameter.^{13,32} Larger lesions, and lesions that involve the skull and dura, can pose significant challenges to treatment.

Many cases of ACC present as a hairless patch of thin skin over the vertex. Small hairless patches can sometimes be confused with conditions other than ACC. ACC affects the skull or dura in about 15 to 30% of cases² (references 5, 6, 8, and 9 in Bharti et al²). Serious morbidity can result if the dura of the superior sagittal sinus is exposed. The exposure of underlying structures can lead to infection, sagittal sinus thrombosis, and/or major hemorrhage from the superior sagittal sinus, which can even lead to death. Hemorrhage can occur if the sinus becomes dry and brittle.² Indeed, one of the cases first described by Campbell was that of an infant who died after bleeding from an exposed superior sagittal sinus.⁸ This rare but known scenario must be recognized by the physician in order to guide treatment and prevent major morbidity (► Fig. 18.2).

18.1.5 Treatment

The treatment of ACC is based on the size and location of the lesions.² Fortunately, most defects are small and relatively superficial. These are effectively managed with local wound care. Large areas with exposed dura can also be safely managed without surgery, but the potential morbidity of these lesions is much greater, and treatment must be monitored carefully.⁶ Conservative treatment requires maintaining a moist environment at all times. Typical dressings include hydrocolloid, petrolatum with or without antibiotic ointment, bacitracin, and silver sulfadiazine. Many authors advocate topical antibiotic ointments to provide both a moist wound-healing environment and, conceptually, prophylaxis against infection and meningitis. If a topical ointment is applied, it should be applied in a thin coat to reduce buildup and reapplied only as needed to main-

tain a moist wound bed. It is important to clean gently any caked or dry emollient from the wound because this layer can create a barrier to the beneficial effects of subsequent medication. Adjuvant treatment with oral or intravenous antibiotics is controversial. There have been reports of adding growth factors (e.g., recombinant human fibroblast growth factor) to the wound to promote further healing, although the need for this is dubious.³³

If larger areas of dura are exposed (> 2 cm²) or circumstances prevent reliable outpatient compliance with dressing (e.g., dysfunctional family dynamics), we strongly recommend hospital admission until the dura is completely covered with granulation tissue. In a neonate, this occurs very rapidly and reduces the likelihood of preventable complications.

Some authors advocate early treatment with allograft and autograft to reduce the scarring associated with spontaneous healing. Apligraf (Novartis, Basel, Switzerland) is a bilayered skin construct formed from allogeneic foreskin keratinocytes and a dermal layer consisting of bovine collagen lattice and human fibroblasts. It has been used but patchy contractures still result, likely from reaction to the bovine component.³⁴ Other skin substitutes, such as those made by Integra (Plainsboro, NJ), have been reported to yield good results.³⁵ The placement of cultured epithelial autografts on the surface of AlloDerm (KCI Lifecell, San Antonio, TX) has also been tried, although the aesthetic outcomes are unknown.³⁶ Coverage with autograft or allograft material may achieve earlier closure of the wounds, but it is unclear if and how these methods can reduce scarring. In our opinion, the lack of evidence to support the superiority of these treatment options over more conservative measures does not justify their relatively high cost.

Although even the largest areas of deficiency will heal if a clean, moist wound environment is maintained, conservative treatment requires constant surveillance and a well-trained and motivated ancillary staff. If this level of care is not available and prolonged observation with local wound care is impractical, one may consider early wound closure to ensure a safer and more predictable outcome, especially if the dura overlying the sagittal sinus is exposed, which can lead to hemorrhage and death. Early closure can be achieved by using various skin substitutes, as noted above, or by rotating local tissue flaps.^{25,37} The

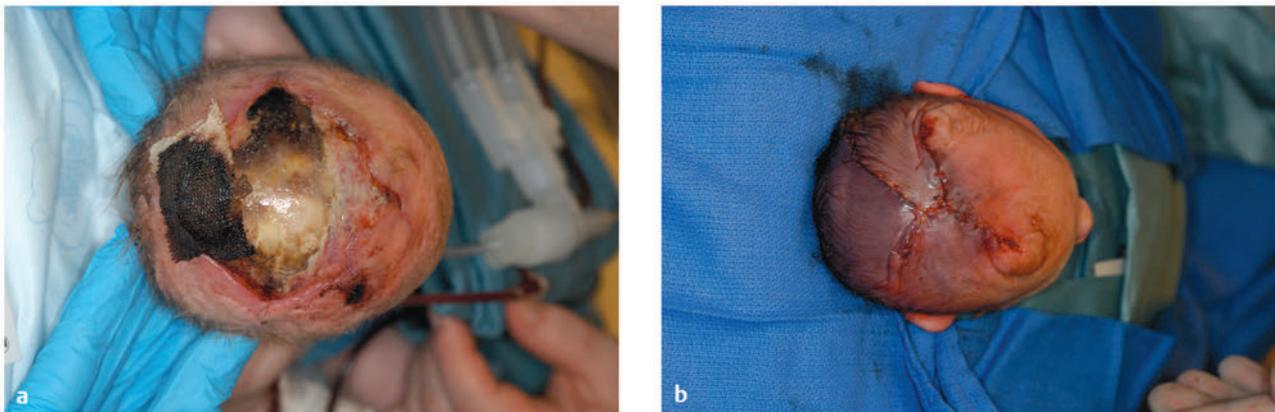


Fig. 18.2 (a) Aplasia cutis congenita with desiccated dura and exposed superior sagittal sinus. This child had a hemorrhage from the superior sagittal sinus shortly after presentation in the intensive care unit and required emergency rotation flap closure. (b) Photograph after closure of defect.

benefit of early closure must be weighed against the potential pitfalls. For example, grafted material can fail to adhere or become infected. Moreover, grafts may be difficult to separate from the underlying dura if later scar excision is planned. Rotational flaps in infants can undergo partial or complete necrosis. Surgical delay should be considered if possible before larger, complex, or multiple-pedicle reconstructions. Some authors have demonstrated good results with the use of composite bone and soft-tissue flaps at a very early age.³⁸

Defects that extend into the deep dermis will leave a scar, and hair will not regrow in these areas. In such instances, many families express an interest in reducing or removing the scar. The timing of this depends on the size of the area of alopecia and whether any underlying bone defect is present. If it is, we recommend deferring any soft-tissue reconstructive procedure until the bone has healed or until the child is at least 2 years of age because little osseous healing can be expected after this time.

The best method of soft-tissue and/or bone reconstruction depends on the size of the defects. Areas of alopecia with a width of up to 2 cm can be addressed with simple excision and closure. Larger areas up to 4 cm in width can also be closed with this method, but more sophisticated techniques are required to mobilize the scalp. Specifically, the scalp must be widely undermined and the galea aggressively scored with multiple releasing incisions. When the ability to close the defect fully is in question, it is advisable to begin with only a single incision along one edge. After mobilization, the tissue excision can be tested by overlapping the edges of the wound and excising the redundant tissue. If the entire scar cannot be excised, the wound is closed, and one can come back in 6 months to a year to complete the excision. This method of serial excision is very effective and can address even very large areas of alopecia. In rare instances in which the area of alopecia is extensive, tissue expansion or rotational flaps should be considered.⁹ The former option requires two procedures and has potential complications, such as infection and expander extrusion or rupture. In very young infants, it also can deform the cranium. The latter option works well if carefully planned. The use of surgical delay is advisable in most instances. Delay involves performing all incisions and elevating, but not rotating or in-setting, the flaps several weeks before the definitive reconstruction. This step significantly improves the perfusion and durability of soft-tissue flaps, especially those with a high length-to-width ratio. It is advisable to seek the help of an experienced reconstructive surgeon before embarking on this treatment path.

Bone defects that are large enough to pose a safety concern (>2 cm²) may warrant grafting. In most cases, the overlying soft tissue is of poor quality, and bony grafting should be done concurrently with the soft-tissue reconstruction to ensure a healthy, vascularized covering for the graft. This can be done with corticocancellous particulate autograft in a younger child or split cranial bone if the child is older.³⁹ We advise against the use of alloplastic materials in pediatric cranial reconstruction because they have higher rates of extrusion and infection than autografts, are very expensive, rarely osseointegrate, and do not grow with the cranium. There are few if any indications for alloplastic cranial reconstruction in the pediatric population.

18.2 Atretic Cephaloceles

18.2.1 Background

Cephaloceles are generally defined as herniations of structures of the cranium through a defect in the skull, and they can have a fairly diverse presentation with associated abnormalities of the brain.^{40,41} Three major types of cephaloceles include encephaloceles, meningoceles, and atretic cephaloceles. These lesions are often defined by their location as either occipital or parietal.⁴² Parietal cephaloceles have been described as having a worse prognosis,⁴² but this has been contradicted elsewhere.⁴¹

Encephaloceles (or meningoencephaloceles) are herniations of the brain and meninges, and children with these malformations often have the worst prognosis for cognitive development. Meningoceleles are herniations of meninges that do not contain cerebral tissue. These lesions are filled with cerebrospinal fluid (CSF) that communicates with the underlying brain via a connection.

Atretic cephaloceles have been described differently by various sources, which can be quite confusing. In general, an atretic cephalocele is a congenital lesion of the scalp and skull consisting of a skin-covered dural sac that may or may not contain fluid. Each lesion generally has a stalk that connects it to the underlying dura. Atretic cephaloceles can be either flat or cystic. We distinguish cystic atretic cephaloceles from meningoceles in that the stalk of an atretic cephalocele usually has a closed lumen, and the cyst fluid does not freely communicate with the underlying brain. On the other hand, meningoceles contain CSF that communicates with the underlying brain.

These lesions can contain rests of glial tissue in addition to meninges.^{41,43} Some may think of the lesions as “burnt-out” or sequestered cephaloceles.⁴⁴ Because they contain neural tissue, they have also been referred to as *heterotopic neural nodules*.⁴⁴ Other authors have used the terms *rudimentary cephaloceles*, *occult cephaloceles*, and *abortive cephaloceles*.^{41–43,45,46}

Atretic cephaloceles have been reported in various studies to comprise 25⁴² to 50%⁴¹ of all cephaloceles.

18.2.2 Causes

Most atretic cephaloceles are thought to be sporadic, but some have been seen in association with underlying genetic syndromes. Walker-Warburg syndrome, or cerebro-ocular dysgenesis–muscular dystrophy syndrome, is a rare autosomal-recessive form of muscular dystrophy.⁴⁷ It is associated with multiple cerebral anomalies, including cephaloceles. A number of other genetic syndromes or familial associations have been described with atretic cephaloceles.^{48–51} In addition, some teratogens have been linked to cephalocele formation.⁴¹

Multiple theories have been proposed to explain the formation of atretic cephaloceles. Some believe that they form when the neural tube fails to close. Others believe that the neural tube closes, then reopens and develops abnormally.⁴¹ Drapkin proposed that atretic cephaloceles form from remnants of the neural crest after faulty migration.⁴³ Yokota et al believed that an atretic cephalocele forms after the involution of a true meningocele in utero.⁴²

18.2.3 Clinical Presentation

Atretic cephaloceles generally present at or near the midline in the parietal or occipital regions, often in the vicinity of the posterior fontanel.⁴³ These lesions can present as a flat bump or as a cystic structure (► Fig. 18.3 and ► Fig. 18.4). They are usually skin-covered, but the skin can be quite thin and may be ulcerated or discolored with a vascular stain.^{41,44} The lesions are often hairless, but a thick ring of hair may surround the lesion, often called the “hair collar” sign.⁵² There is generally an associated bone defect. In one study, the lesions ranged in size from 10 to 35 mm.⁴¹

Various authors have proposed different classifications of these anomalies. Drapkin described how some lesions do not communicate with the underlying cranial cavity, whereas other lesions have fibrous stalks that attach to the dura and extend through a distorted superior sagittal sinus to end in the falx or a deeper location.⁴³ Patients with the latter type of lesion often have a high-riding torcular, upward-coursing straight sinus, and high tentorium.⁴³ Magnetic resonance (MR) imaging can demonstrate these and other venous anomalies and show the vertical positioning of the straight sinus.^{53,54} The association of sinus

pericranii with atretic meningocele has been reported.⁵⁵ A number of underlying cerebral anomalies may be associated with atretic cephaloceles.^{41–43,56} Although the necessity of



Fig. 18.3 Atretic cephalocele with the “hair collar” sign and capillary stain.



Fig. 18.4 (a) Cystic atretic cephalocele demonstrating the “hair collar” sign. (b) Intraoperative photograph shows stalk traversing the cranium. (c) Postoperative photograph after closure. (D) Preoperative sagittal T2-weighted magnetic resonance image shows cystic atretic cephalocele with stalk connecting it to the underlying dura.

preoperative MR imaging has been debated, it can be helpful to detect vascular and cerebral anomalies and may help with the prognosis for cognitive development.

18.2.4 Treatment and Outcome

Atretic cephaloceles are often treated with surgical excision. There is no absolute indication to remove these benign lesions, but uncertainty about the long-term biological behavior of ectopic meningeal tissue seems to support excision. An incision is made perpendicular to the edge of the lesion. Based on the orientation of the lesion, we choose the direction of the incision to correspond to the longest axis of the lesion. After dissection through subcutaneous tissue, blunt dissection is performed circumferentially around the base of the dural sac to find the stalk. The stalk is then ligated and cut. One does not need to dissect the dome of the dural sac because it often fuses with the epithelium. A layer of pericranium can be closed over the dural stalk. Any abnormal or redundant skin should be sharply excised in an elliptical fashion. The galea and skin are then closed in layers.

Cognitive outcome depends on whether the child has underlying cerebral anomalies. Martinez-Lage et al reported that 8 of 16 patients with these lesions showed normal development. It is important to note that 5 of their patients also had Walker-Warburg syndrome,⁴¹ and these presumably had a worse prognosis.

18.3 Parietal Foramina and Cranium Bifidum

18.3.1 Parietal Foramina

A number of calvarial variations are encountered in a typical practice setting (see box “Examples of Morphological Calvarial Variations (p.234)”). The clinical significance of parietal foramina continues to plague parents and the medical community. It is believed to result from a genetic mutation (*MSX2*, *ALX4*) transmitted in autosomal-dominant fashion⁵⁷ and is estimated to occur in fewer than 1 in 25,000 individuals; many familial examples have been reported in the literature.⁵⁸ An association with Saethre–Chotzen syndrome has also been reported in multiple families.^{59,60}

Examples of Morphological Calvarial Variations

- Parietal foramina
- Cranium bifidum (anterior/posterior)
- Supraorbital notch
- Persistent frontal foramen
- Metopic ridging
- Inca bone
- Occipital foramen

Presenting as symmetric calvarial defects on either side of the sagittal suture, parietal foramina are located close to the confluence of the sagittal and lambdoid sutures. The hallmark indicators of smooth, nonsclerotic defects encompassing both tables

of the skull are a direct result of incomplete ossification around the parietal notch, which is normally closed by the fifth month of fetal development. Although generally present at birth, they are not uncommonly discovered at a later stage. Occasionally, they may be associated with meningeal, cortical, and vascular malformations of the posterior fossa, in addition to epilepsy. Fortunately, the defects are relatively small, often less than 2 cm in diameter, and rarely require any surgical correction. With larger defects, associated emissary veins may be present, so that caution is required if surgical repair becomes necessary. The risk for injury after head trauma has been proposed, particularly in light of cases of skull fractures running through preexisting parietal foramina.⁶¹

For larger defects requiring cranial reconstruction, the use of autologous material is best in the long run. Multiple authors have outlined various approaches to this persistent defect but generally recommend autologous constructs, although mesh plating systems as well as hydroxyapatite have been used.^{62,63} Another approach, recently introduced by Rogers et al, involves the use of an exchange cranioplasty in which full-thickness, healthy bone is transferred from an adjacent area to fill the defect.⁶⁴ Particulate outer or inner table bone is used in a fibrin glue (Tisseel; Baxter, Deerfield, IL) suspension. This has been found to offer excellent regrowth potential and avoid difficulties with a dysfunctional osteogenic dural matrix.

18.3.2 Cranium Bifidum

Cranium bifidum, often thought to represent a persistent posterior fontanel, is a midline variant of the bilateral parietal foramina. It has been hypothesized that cranium bifidum and parietal foramina are the same entity, differentiated only by the age at which they manifest.⁶⁵ Cranium bifidum is differentiated by its more anterior location over the vertex, anterior to the intersection of the lambdoid and sagittal sutures.

Although the majority of defects are located posteriorly, the presence of an anterior cranium bifidum is a common component of frontonasal dysplasia and more often requires surgical correction because of its size and location. Examples of intracranial dermoids becoming infected in association with an anteriorly located cranium bifidum have been described; these required surgical dissociation of the nasal compartment from the intracranial contents.⁶⁶ A more classically located cranium bifidum in the posterior calvaria may herald underlying anatomical variations in the posterior fossa, including atypically placed venous sinuses.⁶⁷ Although the majority of cases of cranium bifidum occur in association with other congenital anomalies, including cutaneous dysmorphology, one can also see isolated calvarial defects without associated abnormalities.⁶⁸

18.4 Conclusion

Congenital lesions of the skull and scalp are common and often benign lesions. Treatment ranges from observation to surgical correction with a multidisciplinary team. The conditions discussed in this chapter—ACC, atretic cephaloceles, and parietal foramina/cranium bifidum—are seen in a typical pediatric

neurosurgical practice. Caring for patients with these conditions requires a good understanding of their pathophysiology and the treatment options available.

Pearls

- The treatment of cutis aplasia depends on the size and extent of the defect.
- Many cutis aplasia lesions can be treated conservatively with moist dressings, although they must be watched very closely. If the superior sagittal sinus is exposed, care must be taken to make sure that it does not dry out in order to avoid serious hemorrhage.
- Atretic cephaloceles are often treated with surgical excision.

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19 Craniosynostosis

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Craniosynostosis is the premature closure of one or more sutures of the cranial vault. Early fusion of cranial sutures will generally cause abnormal growth of the cranial vault and skull base, and it may affect brain growth and development.

Physicians as far back as Hippocrates and Galen recognized the relationship of the cranial sutures to skull deformities.¹ By the 16th century, anatomists had described a wide range of cranial deformities associated with premature closure of cranial sutures.¹⁻⁴ Andreas Vesalius, in his work *De Humani Corporis Fabrica*, illustrated both absent sutures and several abnormal skull shapes, which he described in terms of prominences² (► Fig. 19.1). In 1791, von Sommerring was the first to describe bone growth in the skull as occurring primarily at suture lines, and to note that an abnormal head shape would expand in a plane parallel to a fused suture.⁵ In 1851, Virchow first described characteristic abnormal growth patterns with specific synostoses, and he classified the morphological descriptions still used today.⁶ The premise that normal skull growth tends to be in a plane perpendicular to the suture and abnormal growth is parallel to the fused suture is generally called Virchow's law.

As our understanding has progressed, it appears that the relationship between sutures and skull growth is not as straightforward and linear as originally proposed. Moss, in 1959, was the first to appreciate the deterministic effect of the skull base on the cranial vault and proposed that the primary mechanisms driving cranial deformity originated at the cranial base, not the sutures.⁷ He noted that removal of a fused suture did not always alter abnormal skull growth, an observation that contributed to the development of more complex surgical procedures than simple strip craniectomies.

As a result of better understanding of the condition and newer technologies, the surgical treatment for craniosynostosis has

undergone interesting trends. Early suturectomies in the late 19th and early 20th centuries were abandoned because of poor patient selection and a high mortality rate.⁸ In the mid-1900s, suturectomies were again popularized, but outcomes were variable and limited by early refusion and inconsistent results.^{1,9} The theories of Moss, combined with the pioneering work of Tessier in the 1970s, led to extensive cranial vault reconstruction procedures to correct synostosis that remain popular today. However, with new minimally invasive techniques and adjuvant therapies, such as helmets, springs, and internal distractors, a new era of treatment options is emerging.

19.1 Epidemiology and Etiology

Craniosynostosis affects 1 in every 2,000 to 2,500 live births.^{10, 11} Single-suture synostoses are most frequently observed, with an increased frequency seen in children who have non-Hispanic white mothers.^{12,13} The sagittal suture is most commonly involved, accounting for 53 to 60% of all cases of craniosynostosis with a male-to-female ratio of 2:1. Coronal synostosis follows, accounting for 17 to 29% of cases and manifesting twice as frequently with unilateral involvement as with bilateral involvement. Metopic synostosis occurs in 4 to 10% of cases, and lambdoid synostosis is the least common, accounting for fewer than 2% of cases.^{10,14,15} Syndromic craniosynostosis, representing fewer than 5% of all cases, is discussed in a separate chapter.

The etiology of nonsyndromic craniosynostosis is incompletely understood, and most cases appear to be sporadic.¹⁶ Numerous factors have been implicated, ranging from genetic mutations and metabolic and hematologic syndromes to teratogens such as valproic acid and retinoic acid. Maternal smoking and advanced paternal age have also been implicated.¹⁷⁻²⁰ It is likely that a combination of genetic factors and external forces mediates the pathway to suture fusion. More than 100 mutations have been identified in association with craniosynostosis, including mutations of the *FGFR1-3*, *NELL1*, *MSX2*, *TWIST*, and *GLI3* genes.^{11,21} It is unknown how significant a role these genetic anomalies play in the development of synostosis, and genetic and molecular findings have had only minimal clinical impact thus far on the treatment of patients with this problem.

19.2 Physiology and Anatomy

The skull base and cranial vault originate from neural crest cells that surround the enlarging brain. At 5 to 6 weeks of gestation, dural condensations form, and islands of cartilage subsequently develop over the dura. These islands go on to become the osteoblastic ossification centers that form the calvarial bones. The junction of osteogenic fronts forms sutures, best described as sites of bony adaptation rather than as primary growth centers,²² by 16 weeks of gestation. The mechanistic forces that modulate bone growth at the sutures include underlying brain growth, interactions at the dural-calvarial interface, and external mechanical forces.²³⁻²⁵ Supporting a genetic underpinning to the condition, experimental studies have shown that

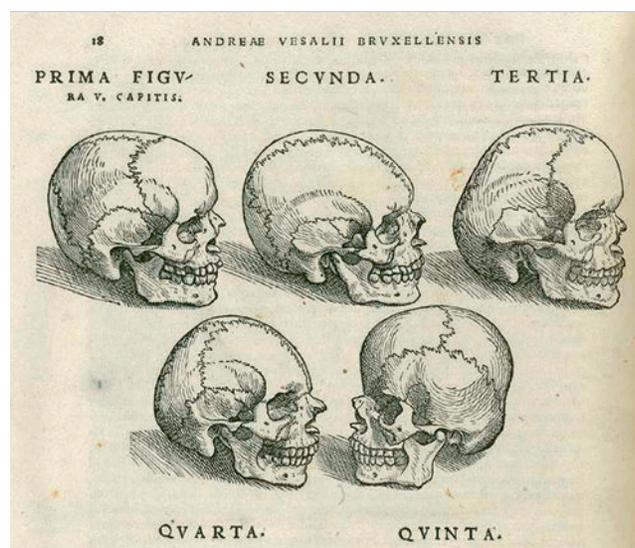


Fig. 19.1 Illustrations of abnormal skull shapes by Andreas Vesalius from *De Humani Corporis Fabrica*. (Courtesy of Oregon Health & Science University.)

compression of a suture, as with an external mechanical force, will cause bone resorption along the suture margin rather than suture fusion.^{26,27} Distraction of a suture, such as with elevated intracranial pressure (ICP), will lead to bone growth along the suture edge, with ensuing enlargement of the calvarial bones and cranial vault. After birth, the cranial vault grows most rapidly during the first year of life, with brain volume doubling during the first 6 months and again by age 2 years. The calvaria then continues to grow in a linear fashion until the age of 6 to 7 years, when growth via sutures is essentially complete.

Virchow's initial hypothesis of skull deformity can be extrapolated to explain the characteristic skull shapes associated with individual forms of craniosynostosis. Delashaw et al redefined the mechanism with the following tenets: two cranial bones connected by a prematurely fused suture will act as a single bone plate, with reduced growth along the margins of that plate, and compensatory skull growth will occur symmetrically along sutures that are in line with a synostotic suture²⁸ (► Fig. 19.2).

19.3 Diagnosis

The diagnosis, management, and treatment of patients with craniosynostosis can be quite variable, depending on the number of sutures involved and the severity of disease. For severe cases or those with syndromic associations like syndactyly, the

initial diagnosis may be established in utero based on morphology. Nonsyndromic craniosynostosis will typically be diagnosed postnatally by observation of a characteristic skull shape. The deformity is generally visible at birth, although occasional mild deformities may be missed. Although the most apparent findings on physical examination will be characteristic calvarial shapes, perisutural ridging may also be noticed. Associated medical conditions, although uncommon in single-suture synostosis, may include midface hypoplasia, deafness, blindness, learning disabilities, speech impairments, swallowing dysfunction, nasopharyngeal airway obstruction, heart and lung abnormalities, and extremity abnormalities.

Radiographic imaging may be used to corroborate the physical examination findings or to rule out an associated intracranial abnormality, although it is rarely needed to establish the diagnosis. It is important to define clearly the questions to be addressed by any imaging and avoid unnecessary studies. Underlying intracranial pathology may be present in a significant number of patients with craniosynostosis,²⁹ although it is not likely to have a major impact on treatment strategies.³⁰

Skull X-rays are frequently obtained when a diagnosis of craniosynostosis is suspected, yet they have minimal diagnostic value beyond that of a detailed physical examination and are often misinterpreted. Three-dimensional computed tomography (CT) provides a comprehensive view of the suture as well as the overall head shape (► Fig. 19.3a,b) and will clearly con-

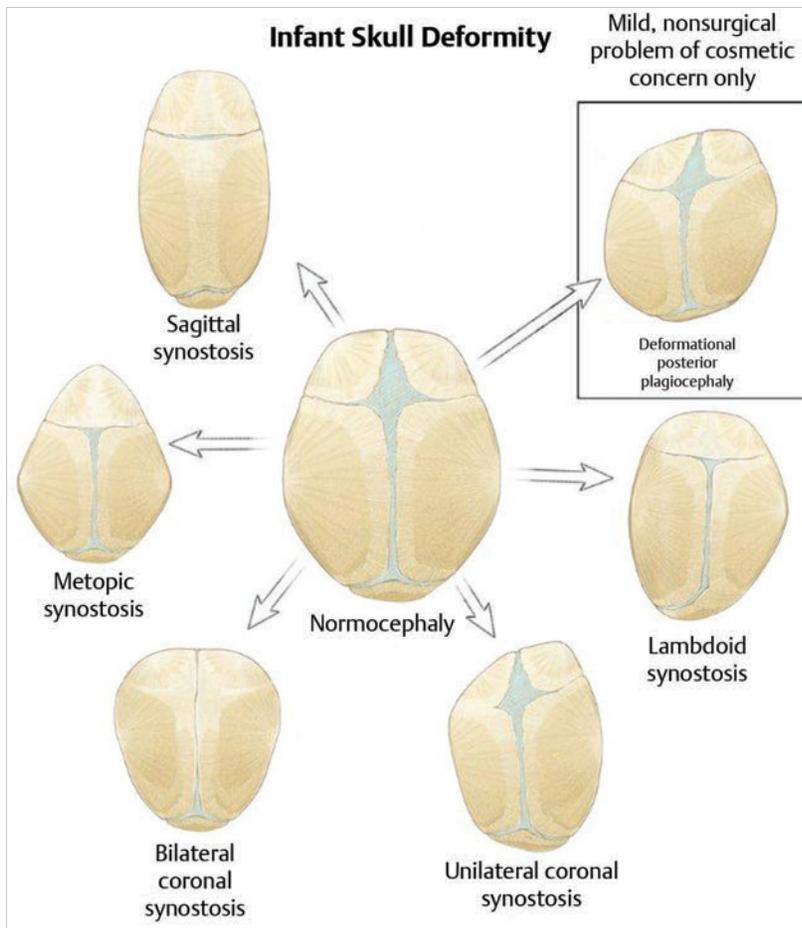


Fig. 19.2 Normal skull anatomy and pathologic skull conditions.

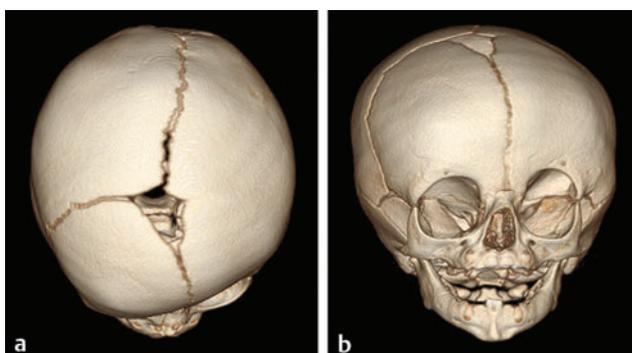


Fig. 19.3 Three-dimensional CT scans in a case of unilateral coronal synostosis showing in exquisite detail both (a) sutural closure and (b) facial deformity.

firm a diagnosis of craniosynostosis, although it should be used judiciously. Exposure to CT has been associated with subsequent malignancies,^{31,32} and all effort should be made to minimize the unnecessary exposure of infants to radiation. Sedation risks will also be added to the potential negative factors associated with neuroimaging. Three-dimensional CT should be reserved for those cases that require visualization of the skull base, involve multiple or complicated suture pathology, or have an unclear diagnosis. If the diagnosis of synostosis is clinically obvious and concern for brain pathology exists, the use of ultrasound or magnetic resonance (MR) imaging should be considered a safer alternative to CT.

19.4 Indications for Surgical Treatment

There is wide variation in the management of craniosynostosis. No definitive data exist to guide optimal timing or type of surgical intervention, and treatment will vary based on age of the patient at presentation, location and number of synostoses, severity of deformity, and ultimately the preferences of the treating surgeon(s). In order to standardize the care of these children, the Centers for Disease Control and Prevention (CDC) brought together international specialists in all associated disciplines to establish and publish parameters of care.^{11,33} Common themes of that document include the complexity of the management of these children and the benefits of multidisciplinary care in craniofacial centers.

The two main indications for the surgical treatment of craniosynostosis are to correct the skull shape for aesthetic and psychosocial considerations and to make certain that there is adequate space for normal brain growth. From an aesthetic perspective, the deformities associated with craniosynostosis are generally progressive for the first year of life, and their social and psychological impact on affected children is in itself sufficiently concerning to justify treatment.³⁴

The relationship between craniosynostosis and brain development is not completely understood. It has been postulated that global intracranial hypertension,^{35–39} focal brain hypoperfusion,^{40–42} and mechanical deformation of neuroanatomical structures^{43–47} may all play varying roles. Studies attempting to demonstrate a relationship between intellectual and behavioral

disabilities and craniosynostosis have had varying and sometimes contradictory results.^{14,46–66} Some data have suggested a benefit to early surgical treatment; however, recent genetic studies have suggested that some genes implicated in craniosynostosis are also essential to brain growth,⁶⁷ and it remains unclear if skull morphology is simply associated with or an influential factor in abnormal brain development.

A study assessing the neurodevelopment of infants both before and after surgical treatment for single-suture craniosynostosis found that developmental testing results were similar after surgical treatment and within a normal range when compared with those of controls.⁶⁴ Surgical timing did not appear to affect patient scores. Although it appears that developmental scores remain generally normal and stable in the perioperative periods, differences become more apparent later in childhood. A recent multicenter study demonstrated consistently lower mean neurodevelopmental scores in 3-year-old children who had been treated for single-suture craniosynostosis when they were compared with controls,⁶⁸ suggesting that these children are at risk for developing cognitive and behavioral disabilities in their school years, regardless of surgical correction.

Although the risk varies depending on the specific diagnosis, a small but significant percentage (4 to 14%) of patients with single-suture synostosis may develop intracranial hypertension,^{35,69,70} and the incidence is as high as 47 to 67% in patients with multiple involved sutures.^{35,69,71} The underlying pathologic mechanism responsible for elevated ICP is likely multifactorial but may include cephalocranial disproportion, venous outflow obstruction, upper airway obstruction, hydrocephalus, and narrowing of the cranial foramina.^{35,70,72–74} Intracranial hypertension may develop gradually, but it should be evident within the first 6 years of life, when brain growth is nearly complete.

The relationship of elevated ICP to cognitive outcomes is unclear. Renier et al performed psychometric testing and invasive ICP monitoring in children with craniosynostosis in a 1989 report from the Hôpital des Enfants Malades in Paris.⁶⁹ Elevated ICP (> 15 mm Hg) was found in 8% of patients with sagittal synostosis, 6% of those with metopic synostosis, and 12% of those with unilateral coronal synostosis. Patients who had multiple fused sutures or who presented after 1 year of age had higher rates of pathologically elevated ICP. A statistically significant relationship was found between ICP and cognitive capacity, with higher ICPs correlated to lower developmental quotients (DQs) and intelligence quotients (IQs). Other relevant reports in the literature have demonstrated improved behavior with resolution of papilledema,^{75,76} improved IQ and developmental progress following cranial vault expansion for documented intracranial hypertension,⁶⁹ and poorer cognitive function in those children with elevated ICP presenting after the age of 3 years.⁶⁹

19.5 Surgical Treatment

Surgical methods for correcting craniosynostosis-related skull deformities have evolved over time, and multiple techniques have been found to have acceptable results. Available data have yet to demonstrate a single best procedure for the treatment of synostosis, which would indicate that there are many acceptable methods for treating the condition. Treatment considera-

tions should include patient age, severity of the disorder, and associated medical conditions. Intervention early in life has the advantage of utilizing the effects of the rapidly growing brain to reshape the skull, along with halting secondary deformities in the face, skull base, or cranial vault that occur over the first year of life. Generally, the procedures in young infants tend to be less invasive, but the increased surgical risk in smaller infants should be considered. Endoscopic techniques in which postoperative helmets are used to direct skull growth are generally best performed by 3 to 6 months of age, whereas spring- or distractor-mediated techniques can be used in older infants, as brain growth is no longer the driver of skull growth. Open cranial vault remodeling procedures are often delayed until 6 to 12 months because they are associated with greater blood loss and longer operative times, and many surgeons have observed an increased incidence of revision surgery in patients operated on before 6 months. Treatment options become more limited as a child grows older, and therefore early diagnosis and referral to a craniofacial center are important.

19.5.1 Open Reconstructions

In the 1970s, Tessier pioneered the technique that remains the standard of care to this day.^{77,78} Extensive surgical reconstruction was performed during which large segments of cranium were removed, remodeled, and stabilized with rigid fixation. This procedure had the advantages of establishing the desired skull shape and size intraoperatively, and of achieving predictable immediate outcomes. Disadvantages to these open procedures include significant blood loss, lengthy surgical times and hospital stays, and frequent need for postoperative intensive care unit monitoring. Because surgery is usually delayed until the patient is older in order to minimize operative morbidity, the cranial deformities can become more severe before intervention. The manipulation of large segments of the skull also disrupts the dural-calvarial interface, which may affect future growth and lead to less predictable results over time.

19.5.2 Minimally Invasive and Endoscopic Surgery

Endoscopic and minimally invasive treatments for craniosynostosis are growing in both popularity and demand by patients' families. Although early suture release surgeries failed to correct cranial deformities in a substantial percentage of patients because of rapid sutural refusion, external orthoses, internal springs, and distractors have negated this problem. Barone and Jimenez published their initial experience with endoscopic suturectomy and adjunctive postoperative orthotic treatment in 1999,⁷⁹ and their data have been supported by others.⁸⁰⁻⁸² In comparison with conventional open cranial vault remodeling, there are significant reductions in blood loss and need for transfusions, smaller incisions, shorter surgical times, shorter hospital stays, and overall decreased hospital costs. The smaller operations are more limited in spectrum, however, and older patients or those with severe cranial deformities may not be candidates.

The benefit of shorter operative times in these procedures may be profound; a recent report from Naumann et al demonstrated lower mean neurodevelopmental scores among children who had undergone lengthier operations and had greater exposure to inhaled anesthetics for cranial vault surgery for single-suture craniosynostosis during infancy.⁸³

Postoperative skull-molding helmets are most commonly used as an adjunct to endoscopic strip craniectomies. Helmets have the advantage of being adjustable over time, and they have the capacity to modify skull growth in three dimensions. However, they are less effective in infants older than 3 to 6 months. Springs and distractors have the disadvantage of requiring an additional operation to remove them, but they allow predictable advancements in a single plane of growth and also can be used in older children because brain growth is no longer the essential driver of skull growth.

Regardless of surgical techniques, long-term follow-up is important in children treated for craniosynostosis; it should include observation of cranial vault growth and morphology as well as of neurocognitive and psychosocial development until at least 6 years of age.^{11,33} Perhaps the most useful tool for following a child with craniosynostosis is head circumference. If the growth rate falls, deformity recurs, or clinical symptoms ensue, the child should be evaluated with appropriate imaging studies and an ophthalmologic evaluation. Adjunct procedures may be necessary in a subpopulation of these patients, regardless of the type of initial treatment.

19.5.3 Surgical Techniques

The technique for surgical reconstruction should be tailored to the type of synostosis and the age of the patient, and each surgeon will develop certain nuances in the way the procedures are performed. Interestingly, despite the relatively wide variations in phenotypic presentations, the surgical approaches have many similarities. It would be beyond the scope of this chapter to describe each technique for each type of synostosis in great detail, as authors have described literally dozens of variations for each suture type. However, there are many broad concepts that are important for both minimally invasive and open techniques that are discussed here, with the salient features for particular sutures covered in the individual sections that follow.

Endoscopic Techniques

Like that of open suturectomy in the past, the main goal of minimally invasive techniques is to release the fused suture (s) without an attempt at major reconstruction or contour change at the time of surgery. This is especially true for metopic, coronal, and lambdoid sutures and also can hold true for sagittal synostosis, although some authors recommend fairly wide vertex craniectomy and parietal barrel staving for this condition. The incisions are generally limited to 2 cm, and it is important to avoid wide dissection of the soft tissues so as to avoid unnecessary bleeding. Bur holes are placed with a high-speed drill and then locally enlarged with a Kerrison rongeur. Once this is achieved, the periosteum is stripped from the outer surface of the bone, and the endoscope is used to strip the dura from the undersurface of the fused suture. The surgery is made particularly feasible by the

ease with which dura separates from a fused suture. Finally, the craniectomy may be completed with heavy scissors, ultrasonic bone aspirators, or a high-speed drill. Bone edges can then be coated with wax or Gelfoam, with a pressure dressing placed after wound closure for several hours. Despite concerns about the risks for uncontrolled bleeding from torn venous sinuses, the experience of multiple authors has clearly shown this to be a safe technique with a much lower risk for bleeding than open operations.^{79,80,82,84} Within 1 week of the procedure, the infant is fitted with a cranial molding helmet. An orthotist and the craniofacial team follow the patient closely and make necessary adjustments to the helmet until the desired phenotype is achieved or the infant reaches 1 year of age.

Open Cranial Vault Reconstruction

These operations, pioneered by Tessier in the 1970s, are by and large variations of similar procedures. Indeed, metopic and coronal suture operations are very similar variations of what is commonly referred to as the fronto-orbital advancement. The patient is placed supine—except in the case of some types of sagittal synostosis, when a more posterior correction is anticipated—with the head stabilized in a horse-shoe headrest. In all cases, the cranium is accessed via a bicoronal skin incision, which gives excellent access to any portion of the skull and is more cosmetically acceptable than a bifrontal incision. A zigzag incision is used in order to minimize the visibility of incisional scalp alopecia. Minimal hair shave tends to be necessary. Incisions in the anteroposterior plane, occasionally used for sagittal synostosis, are very difficult to work with if revision surgery is ever needed. The anterior and posterior scalp flaps are dissected in the subperiosteal plane to prevent anchoring of bone to periosteal tissue. The dissection is carried forward into the subperiosteal plane in order to allow bilateral orbital rim osteotomies. Once the skull is accessed, all cranial vault surgeries require the removal of large sections of bone to be replaced in a more anatomically normal position, either homotopically (bone replaced to a similar location) or heterotopically (segments of bone moved to different parts of the skull), based on the surgeon's preference. Bone is removed with high-speed drills, and the rate of dural tears should be low because of the integrity of the dura in children. Sagittal saws and osteotomes are useful for removal of the orbital bandeau, which requires cuts through the frontozygomatic process, roof of the orbits, and nasofrontal junction. Blood loss is often steady, but hemostasis should be achieved with the selective coagulation of emissary veins and the application of wax on bone edges. The advent of absorbable plates truly has simplified the surgery by making secure bone replacement readily achievable. Most commercially available plates resorb in 1 to 2 years. Titanium plates should not be used in infants, as they will migrate intracranially as the skull grows.^{85,86} Once all bone is secured, it is advisable to fill bone gaps with the patient's own bone, often a particulate mixture taken from the inner cortical surface, as gaps often will not fill on their own.^{87,88} The incision is then closed with a subgaleal drain, and pressure wrap head dressing is applied. The specifics by suture site are discussed below.

Metopic Synostosis

Clinical Features

Metopic synostosis leads to a characteristic triangular skull morphology known as trigonocephaly. Severe cases will demonstrate ridging of the metopic suture (“keel” forehead), posterior displacement of the superolateral orbital rims, hypotelorism, flattening of the frontal bones, anterior displacement of the coronal sutures, compensatory bulging of the parieto-occipital region, and temporal narrowing. Normal closure of the metopic suture occurs by 9 months, although physiologic closure can occur as early as 3 months, and not all children with premature closure will develop trigonocephaly. Patients who present with only mild ridging of the suture are best treated with conservative measures only. Trigonocephaly has the highest rate of associated cognitive impairment among the single-suture synostoses.

Open Surgical Techniques

As described above, fronto-orbital advancement is used to normalize the forehead and remodel the supraorbital rim. A bifrontal craniotomy is performed with the posterior extent to the coronal suture. The orbital bar is removed in one piece and reconstructed into a more convex configuration with a midline osteotomy if necessary. To correct hypotelorism, the orbital bandeau can be widened with insertion of a bone strut between the two halves. The reshaped orbital rim is then fixed to the nasal bone and angled forward at the frontozygomatic suture.

The frontal bones are split along the midline and replaced in a widened fashion, with radial barrel staves used as needed to widen it. The remaining temporal parietal region should be barrel-staved and fractured laterally to flare out and match the newly replaced frontal bones.

Endoscopic Techniques

Infants younger than 6 months with trigonocephaly may be considered for an endoscopic strip craniectomy. In general, the results are quite good, although the ultimate frontal bone projection often falls slightly short of that achieved with the traditional fronto-orbital advancement.⁸⁰ For a metopic procedure, the patient is placed supine with the head stabilized on a horse-shoe headrest. One midline incision approximately 1.5 to 2.5 cm in length is made just posterior to the hairline, with an orientation perpendicular to the metopic suture (► Fig. 19.4). Often, two emissary veins will be encountered when the dura is stripped, but these are easily coagulated with bipolar cautery and divided. After the craniectomy, the ultrasonic bone aspirator is helpful in reaching around the frontal curvature to ensure that sufficient bone is removed at the nasofrontal juncture.

Outcome

The long-term outcome with open reconstruction is excellent in more than 90% of patients with nonsyndromic metopic synostosis.^{89–94} Should new metopic ridging or progressive frontal towering occur, additional surgery may be required, but rates for this are very low.⁹⁵ Endoscopic outcomes are also excellent, with effective treatment of the midline ridge and gradual



Fig. 19.4 Positioning of a child for endoscopic release of metopic synostosis.

improvement of the paramidline ridges.^{80,96} The correction of superolateral orbital rim retrusion is often not as significant as what can be achieved with an open procedure, but family satisfaction is very high.

Unilateral Coronal Synostosis

Clinical Features

Unilateral coronal synostosis manifests as anterior plagiocephaly. It has several characteristic deformities, including a flattened ipsilateral frontal bone with compensatory overgrowth at the contralateral orbit. Other ipsilateral findings include a palpable perisutural ridge, bulging of the ipsilateral squamous temporal bone, anterior displacement of the ear in comparison with the contralateral ear, shortening of the ipsilateral anterior cranial fossa, narrowing of the ipsilateral mediolateral orbital dimension, and the harlequin deformity. The harlequin deformity is pathognomonic for coronal synostosis and is seen on radiographs because of the elevation of the sphenoid wing. Bulging of the contralateral frontal and parietal bones can be seen. The nasal radix will be deviated toward the side of the synostosis (► Fig. 19.3 and ► Fig. 19.5).

Strabismus is a common associated finding and can be found in 50 to 60% of patients with coronal synostosis.^{97,98} The shortening of the anterior skull base results in a posteri-

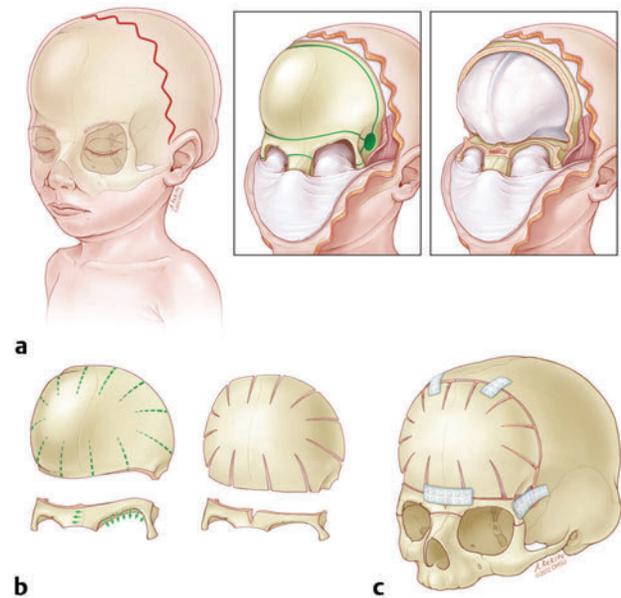


Fig. 19.5 Surgical repair of unilateral coronal synostosis by fronto-orbital advancement. (a) Bicoronal zigzag incision, subperiosteal scalp elevation, and bifrontal craniotomy are performed. The orbital bandeau is removed in one piece. (b) The bifrontal bone is reshaped. The orbital bar is contoured and advanced to equalize projection. (c) The contoured bifrontal bone flap and orbital bandeau are secured with absorbable plates.

orly displaced orbital roof and trochlea, which leads to imbalance at the superior oblique muscle, thus compromising its function. Although surgical correction of the cranial deformity occasionally improves the strabismus, ophthalmologic surgery is frequently needed to address this issue definitively.

Open Operative Technique

Bifronto-orbital advancement with advancement of the ipsilateral orbit is undertaken to achieve orbital normalization and the cosmetic correction of deformity (► Fig. 19.5). The general technique is described above. It is often difficult to create good long-term symmetry in these cases, and because of irregular growth over time, hypercorrection is often performed. Whereas the goal is to create orbital rim symmetry, the affected side is often advanced several millimeters in comparison with the normal side. The deviated nasal radix can also be corrected; it often does not effectively correct over time if not addressed at surgery.

Endoscopic Technique

Severe asymmetry in cases of unilateral coronal synostosis is best treated endoscopically when the patient is younger than 3 months. One 1.5- to 2.5-cm incision is made at the midsuture region in a perpendicular orientation to the coronal suture. The remainder of the technique is identical to that described above, with bone removal from anterior fontanel to the lateral canthus, and patients are similarly fitted with a cranial molding helmet in the first postoperative week.

Outcome

The majority of patients who undergo bilateral fronto-orbital advancement for unilateral coronal synostosis demonstrate an initial significant improvement in cranial shape and have excellent long-term outcomes.^{99–101}

Endoscopic treatment of unilateral coronal synostosis yields excellent outcomes, especially in regard to the nasal root deviation, facial asymmetry, and orbital dystopia.^{80,96} A trend toward a reduction in associated ophthalmologic findings was observed in a recent series published from our institution.¹⁰² Forehead symmetry was significantly improved. Although early results show that fronto-orbital advancement yields slightly better forehead symmetry, the growth patterns after endoscopy appear more normalized over time. Comparison of endoscopic and open techniques with three-dimensional photogrammetry demonstrated statistically significant improvement in facial symmetry in the endoscopic group.⁸⁰

Bilateral Coronal Synostosis

Clinical Features

Bilateral coronal synostosis manifests as brachycephaly with a widened biparietal diameter and frontal towering (turricephaly). Ridging of the coronal sutures is noted, along with flattening of the caudal frontal bone, recessed supraorbital ridges, and bulging of the cephalic frontal bones. The occiput is flattened, and the temporal squamous bones are protruded. Bilateral harlequin deformities can be seen radiographically, and the anterior cranial fossa is shortened bilaterally.

Open Operative Technique

Bilateral coronal synostosis is associated with abnormalities in both the anterior and posterior regions of the skull, and the surgeon must decide if both need to be addressed. For patients with nonsyndromic coronal synostosis, the occipital region is generally not problematic, and the general approach is a fronto-orbital advancement. If attention will be paid to the occipital regions, precautions should be taken, because these children can have issues with stability of the cervical spine or a Chiari malformation.

Techniques for the fronto-orbital advancement are really identical to those described above, with the major goal being advancement of the orbit and frontal bones about 1 cm anterior to the globes. Correction of turricephaly can be difficult and reduction of height can place patient at risk for ICP issues, so this should be done only by surgeons with experience in these procedures.

Endoscopic Technique

The surgical approach to the bilateral endoscopic release of coronal synostosis is simply to perform the unilateral operation on both sides. Early surgery seems to obtain good correction of turribrachycephaly and avoids the secondary turricephaly that ensues over the first year of life in patients whose condition remains uncorrected. Forehead projection is subjectively less

dramatic than with traditional fronto-orbital advancement, in our experience.⁸⁰

Outcome

Initial significant improvement is generally observed in these children after open procedures and endoscopic procedures; however, second surgeries are more common in this group, likely because of the frequent syndromic association.^{103–105} Subsequent development of elevated ICP has also been observed in this population, and patients should be monitored closely for this reason.

Sagittal Synostosis

Clinical Features

Sagittal synostosis is the most common single-suture craniosynostosis. It manifests with a narrow, elongated skull shape known as scaphocephaly (or dolichocephaly). Patients with sagittal synostosis should be screened for signs of intracranial hypertension, especially those who present in later childhood. The degree of deformity should not be reassuring because it does not seem to correspond to the risk for elevated ICP. The region of the suture with the greatest premature fusion will determine whether frontal or occipital bossing, or a combination of the two, is present. Sagittal synostosis is also characterized by perisutural ridging, premature or occasionally delayed closure of the anterior fontanel, and biparietal narrowing.

Open Operative Technique

There are as many open techniques for this procedure as there are surgeons doing the operation. The basic tenets should be to increase the width of the skull and leave the length relatively neutral so as to avoid decreasing the intracranial volume. The surgeon needs to decide if the deformity should be addressed mostly anteriorly, mostly posteriorly, or both anteriorly and posteriorly. The orbital ridge does not require exposure because no significant orbital anomalies are typically seen in sagittal synostosis.

Endoscopic Technique

More than for any other suture, endoscopic treatment of sagittal synostosis has proved to be very effective and is becoming the treatment of choice at many institutions. Patients are positioned prone in a specialized headrest (DORO Horseshoe Headrest; pro med instruments [PMI], Freiberg, Germany) that keeps the head extended (► Fig. 19.6). The torso rests on chest rolls. Two 1.5- to 2.5-cm incisions are made perpendicular to the sagittal suture in the midline. One is placed just posterior to the coronal suture and the other just anterior to the junction of the lambdoid sutures. The subsequent technique is identical to that described above. A cranial molding helmet is fitted during the first postoperative week.

Outcome

Almost all surgical techniques for treating sagittal synostosis report acceptable cosmetic outcomes; however, comparing

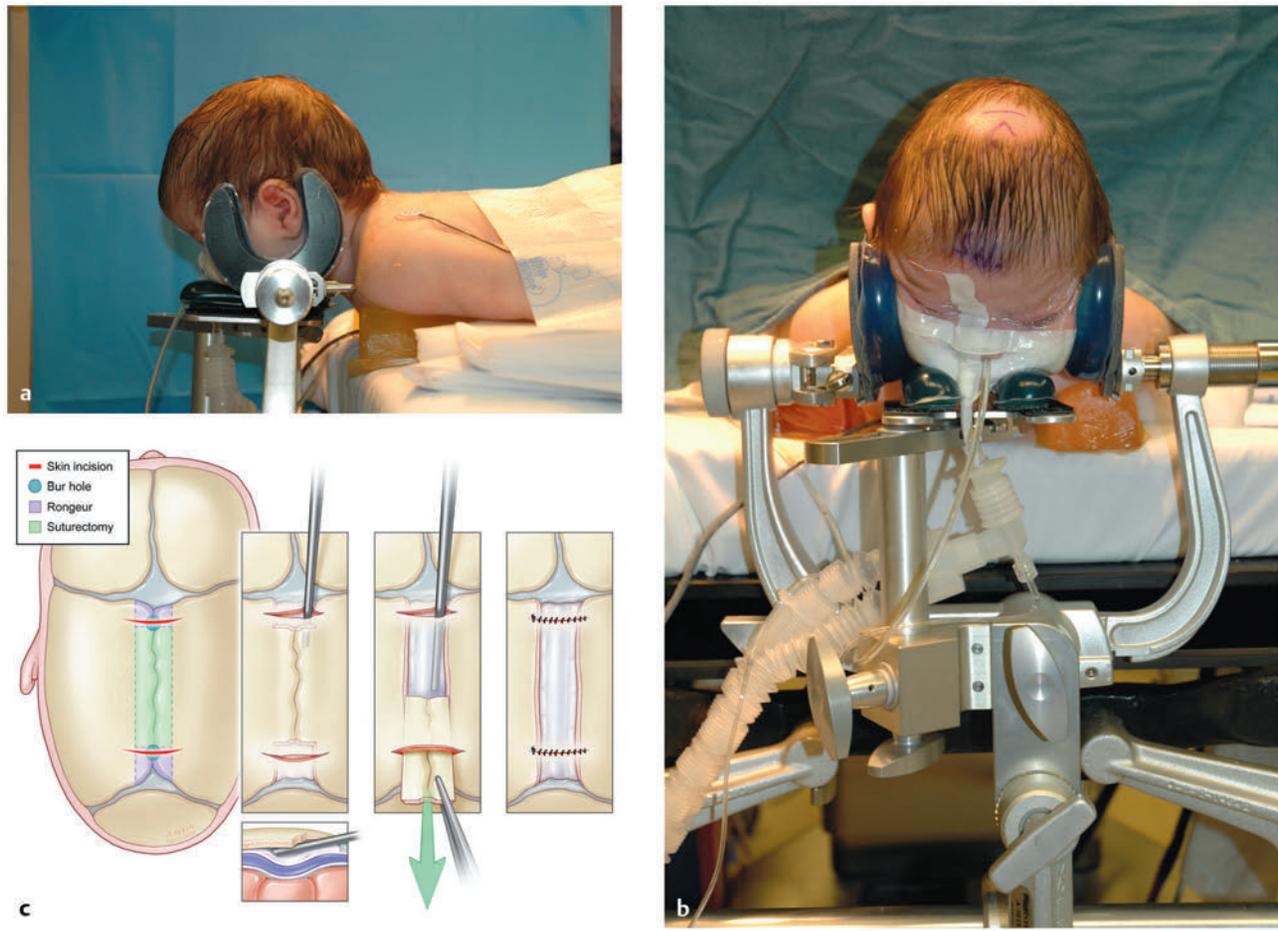


Fig. 19.6 (a,b) Positioning and (c) surgical technique for endoscopic removal of a sagittal suture.

these techniques is difficult without available prospective or long-term data.^{29,106–109} Endoscopic outcomes for sagittal synostosis demonstrate excellent cosmetic correction.^{79,80,82,84} Data demonstrate the age at surgery to be an independent variable for change in the cranial index and increase in the head circumference percentile, and it is best to intervene before the age of 3 months.⁸⁰

Lambdoid Synostosis

Clinical Features

Lambdoid synostosis manifests as posterior plagiocephaly, with associated flattening of the parietal and occipital regions ipsilateral to the fused suture. Differentiating lambdoid synostosis from positional plagiocephaly is critical for determining the appropriate course of treatment for a patient (► Fig. 19.7). Significant morphological differences exist between these two entities, and an accurate diagnosis can usually be made based on the physical findings alone. The head of a child with lambdoid synostosis has a characteristic trapezoid shape, with a posteriorly and inferiorly displaced ipsilateral ear and contralateral occipital bossing. Conversely, positional plagiocephaly is associated with a head that has a parallelogram shape, with anterior

displacement of the ipsilateral ear and associated ipsilateral frontal bossing. The sequelae of lambdoid synostosis can be quite diffuse; the skull has a classic windswept appearance when it is viewed in a coronal plane.

Open Operative Technique

A number of different surgical techniques have been proposed for the treatment of lambdoid synostosis. The selected procedure should be individualized according to the manifested cranial deformities. Surgical objectives should include release of the fused suture and normalization of the posterior cranial vault. Most deformities can be corrected with the patient in the prone position and remodeling of the occipital bone alone. In those patients with significant compensatory changes in the frontal and parietal regions, an extended reconstruction of the calvaria can be undertaken, but it is very difficult to correct the protean manifestations of this disorder, and a “perfect” correction should probably not be the goal.

Endoscopic Technique

For the endoscopic treatment of lambdoid synostosis, the patient is placed prone and the horseshoe head holder is used.

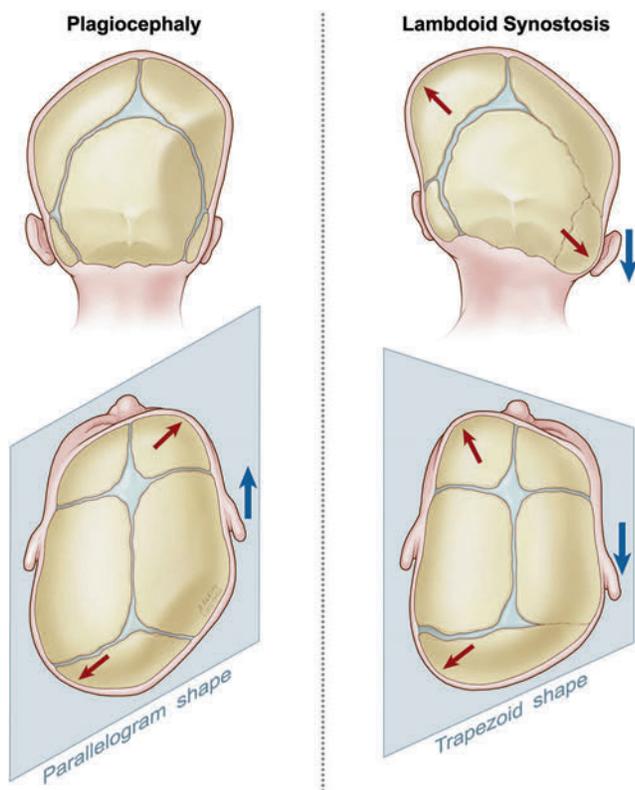


Fig. 19.7 Differentiating lambdoid synostosis from deformation plagiocephaly.

Two 2-cm incisions are made at either end of the suture. The subsequent technique is identical to that previously described. A cranial molding helmet is fitted during the first postoperative week.

Outcomes

Satisfactory results with normalization of the posterior cranial vault are seen in most infants.^{110–112} The remainder of the secondary deformity is very difficult to correct. Endoscopic results, interestingly, seem to afford better correction of the secondary skull deformity in our limited experience, likely because of the younger age at surgery.⁸⁰

19.6 Treatment Alternatives

Spontaneous resolution of a cranial abnormality without surgical intervention is unlikely in cases of craniosynostosis, making observation an inappropriate alternative in the majority of cases. In a patient who has a single-suture synostosis associated with a mild deformity that is cosmetically acceptable, especially in an older child for whom an early diagnosis was not established, conservative management may be considered. Mild deformity should not necessarily reassure the surgeon regarding brain development issues because severity does not correspond to neurodevelopmental outcomes.¹¹³

Orthotic molding has been proposed as an alternative treatment for mild cases of craniosynostosis, with the argu-

ment that helmeting is safer than surgical intervention.¹¹⁴ Until more is understood, we feel that undertaking a treatment that reduces growth in a second plane in a child who already has limited growth in another plane is an inappropriate alternative.

19.7 Complications

The importance of a skilled team, and anesthesiologists who understand the complexity of the cases, cannot be overstated. Craniosynostosis procedures are generally quite safe, with overall low morbidity and mortality rates, but tragedies are possible when the baby is not adequately resuscitated. Blood loss is the most frequently encountered complication associated with the surgical treatment of craniosynostosis. Young patients have low circulating blood volumes, and the amount of blood lost may be deceptively small when slow but persistent bleeding occurs throughout a case. A recent study has found that using tranexamic acid can significantly reduce blood loss and blood transfusion rates.¹¹⁵ Additionally, massive hemorrhage may occur with injury to a venous sinus. Adequate preparation for and monitoring of blood loss is critical in all craniosynostosis procedures. Air embolus is another serious complication that can occur in these procedures. The extensive bony work involved, along with the vascular nature of bone in young children, may lead to the incorporation of air into the vascular system. Monitoring for air emboli should be a routine component of anesthesia for these cases. Elevations in ICP may be seen in patients undergoing a reduction in skull height, and therefore this maneuver should be performed only by surgeons who truly understand the condition.

Other complications that have been observed in these procedures include transfusion reactions, complications related to anesthesia, wound infections, dural injuries, cerebrospinal fluid leakage, injury to underlying brain parenchyma, post-traumatic encephaloceles, orbital or neural injuries, postoperative hematomas, post-reconstruction calvarial defects, and seizure.

19.8 Prognostic Factors and Outcomes

Most children with nonsyndromic craniosynostosis lead normal lives after surgery. As a specialty, we have failed to develop good outcome measures for comparing the cosmetic benefits of different procedures, and we also lack neurodevelopmental outcome studies. National databases will go a long way to rectify this situation, and the parameters of care document developed by the CDC should serve as a good first step. Most neuropsychologists believe that the developmental outcomes are more profound than previously thought, and these children are not adequately studied in that regard. Perhaps the greatest service we can do for our patients is to realize that the effects of their condition may be more complicated and prolonged than originally realized, and to follow them at least until the completion of brain growth, toward 6 to 7 years of age, and longer if needed.

The specialty has also clearly gravitated toward referral to centers of excellence because the problems of these children are not as uncomplicated as previously thought. The parameters of care document outlines a master plan for following patients with craniosynostosis from the prenatal period onward.^{11,33}

Pearls

- Fused cranial sutures lead to abnormal growth of the cranial vault. Virchow’s law states that skull growth will be inhibited in the plane perpendicular to the affected suture, while compensatory growth will be enhanced in a plan parallel to it.
- Differentiating craniosynostosis from positional plagiocephaly is critical when appropriate management strategies are being determined.
- Multiple techniques are available for the surgical treatment of craniosynostosis depending on the patient’s age, severity of the deformity, and preference of the family and surgical team.
- The management of these patients can be complicated, and referral to centers of excellence should be considered.

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20 Craniofacial Syndromes

Richard Hayward

The craniofacial syndromes are a heterogeneous group of rare conditions in which premature suture closure (craniosynostosis) occurs alongside other manifestations of disordered craniofacial development,¹ as well as additional skeletal abnormalities that include, in particular, those of the hands and feet.^{2,3}

The conditions seen most frequently are the eponymous syndromes of Crouzon, Apert, Pfeiffer, Saethre-Chotzen, Muenke (*FGFR3*-associated synostosis), and Carpenter, as well as craniofrontonasal dysplasia. Less commonly encountered are Antley-Bixler,^{4,5} Jackson-Weiss,⁶ and Boston-type syndromes.

The aim of care is to ensure that affected children realize their full developmental potential. Although a major component of treatment is surgical, there is now greater recognition of the needs of the child as a whole. The centers best equipped to achieve this are those that can field a multidisciplinary team; in addition to neurosurgeons, plastic surgeons, and maxillofacial surgeons, such teams include specialists in otorhinolaryngology (ear–nose–throat) and audiology, genetics, pediatrics, neurology, psychology, orthodontics, respiratory medicine, speech therapy, ophthalmology, and, of course, pediatrics—all experienced in the management of the complex problems these children so frequently have.⁷

After a brief account of the syndromes and their genetic basis, this chapter describes first the principles of management and then the complications that affected children are at particular risk for. It ends with a description of the surgical procedures most commonly deployed in the treatment of children with these complex problems.

20.1 The Syndromes

It was hoped that when the genetic basis for many of the craniofacial syndromes was discovered in the 1990s that their classification would change from the one based on the eponymous nomenclature that had been in use for so many years. Unfortunately, the situation proved to be more complex, as the genetic “overlap” between Crouzon syndrome and Pfeiffer syndrome demonstrates—a single mutation is capable of causing both Pfeiffer syndrome and Crouzon syndrome, and mutations on either of two chromosomes are responsible for Pfeiffer syndrome.^{8–10}

It therefore remains important for clinicians to recognize the typical features of each syndrome as traditionally described as well as be conversant with the underlying genetic mutations when these are known.

20.1.1 Crouzon Syndrome

Crouzon described the syndrome that bears his name in 1912. One of the more frequently encountered craniosynostosis syndromes,¹¹ it is transmitted as an autosomal-dominant condition (as with Apert syndrome, there is a significant influence of increased paternal age),¹² although it occurs with nearly equal frequency as a new mutation.

Typical features include a retruded maxilla that leaves the lower teeth projecting anterior to the upper teeth (class 3 malocclusion), a “beaky” nose, a recessed frontal region (brachycephaly) due to bicoronal synostosis, and prominent eyes (exorbitism) due to the combined recession of the infra- and supra-orbital regions (► Fig. 20.1).

Its expression is highly variable, ranging from severe exorbitism with midface retrusion and airway obstruction at one extreme to a mild prominence of the eyes at the other. The degree of craniosynostosis also varies, although the coronal sutures are most commonly affected. A catch for the unwary is that suture fusions need not be present at birth but may appear during the first 2 years of life,¹³ with a high risk for the development of raised intracranial pressure (ICP).¹⁴

Extracranial manifestations¹⁵ seen in severe cases include various types of predominantly cervical vertebral fusion^{16,17} and ankylosis affecting particularly the elbows.¹⁷

A genetically distinct type of Crouzon syndrome is associated with rugated, thickened skin and hyperpigmentation affecting particularly the flexure creases—acanthosis nigricans.¹⁸

Intelligence may be normal in children with Crouzon syndrome, but the more severe the phenotype, the more likely the child is to have developmental and learning difficulties. Marked intellectual compromise was present in 3% in the series of Kreiborg.¹⁹

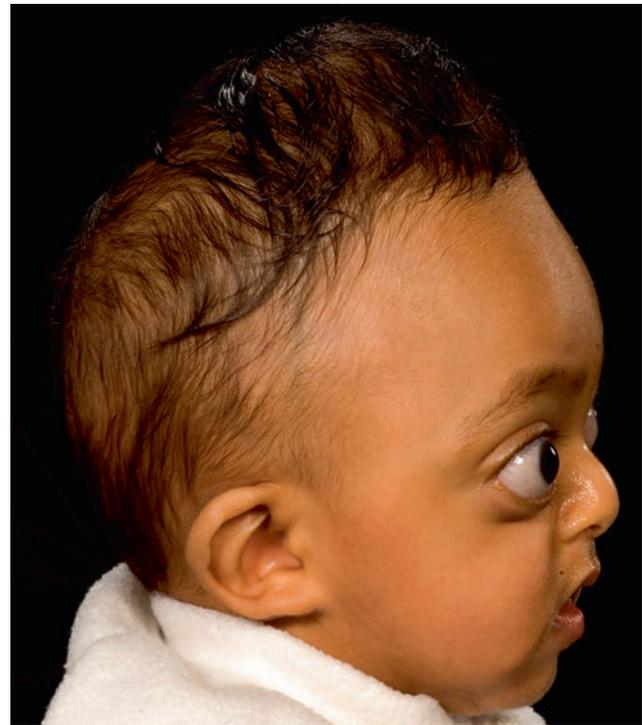


Fig. 20.1 Crouzon syndrome.

20.1.2 Apert Syndrome

Apert described the rare²⁰ condition that now bears his name in 1906.

The affected child has a head that is tall and shortened from front to back (turribrachycephaly) combined with midfacial (maxillary) retrusion, proptosis, a downward cant to the palpebral fissures, and hypertelorism²¹ (► Fig. 20.2a). The essential clinical feature, however, is complex fusion (syndactyly) of the fingers and toes^{22–24} that may require frequent surgical procedures before functional effectiveness is achieved²⁵ (► Fig. 20.2b). Visceral²⁶ and cutaneous²⁷ abnormalities can also occur.

At birth, the child with Apert syndrome may have fusion of only the coronal sutures, while the sagittal and (in particular) the metopic sutures are widely open. Fusion of all sutures, however, is progressive and usually complete before the age of 2 years.

Palatal abnormalities²⁸ ranging in severity from frank clefts to bifid uvula are common and occur with a frequency of up to 75%.^{29,30}

Cervical vertebral fusions that, like the suture fusions, are often progressive occur in more than half of affected children, although it is unusual for them to become clinically significant.³¹

Developmental and learning difficulties are the norm, although a combination of developmental assessments designed for non-Apert children with low societal expectations may overestimate their severity.³² Although a small percentage of children may complete secondary education (usually only with assistance), many drop out of mainstream education during their primary school years, and a small percentage are too severely

affected to participate in the mainstream education system at anything above kindergarten level.^{33,34} The long-term study of Allam et al of the treatment of Apert syndrome includes a description of the eventual social integration of these children.³⁵

20.1.3 Pfeiffer Syndrome

Pfeiffer syndrome is an autosomal-dominant craniosynostosis-associated syndrome characterized by suture fusions that range from bicoronal synostosis alone to pan-synostosis (with or without the cloverleaf skull deformity; see below).³⁶ Those affected have digital abnormalities,³ such as curved and shortened thumbs and great toes³⁷ (► Fig. 20.3), and (less commonly) digital fusions (but of a lesser degree than those seen in Apert syndrome³).

Cohen³⁸ divided Pfeiffer syndrome into three types based on clinical severity. Children with type 1, those least affected, may display little more than bicoronal synostosis and midface retrusion (in addition to their digital abnormalities) (► Fig. 20.4). Their neurocognitive development may be unaffected, particularly if early complications have been aggressively treated.³⁹

In types 2 and 3 Pfeiffer syndrome, the degree of midface and frontal retrusion is severe enough to obstruct the upper airway and cause ocular protrusion sufficient to threaten the corneas (► Fig. 20.5). The shortening of the skull base and crowding of the posterior fossa due to the bilateral lambdoid component of the pan-synostosis produces an increased risk for hydrocephalus. Ankylosis (bony and soft tissue) of the elbows¹⁷ and knees is common, as are fusions of the cervical vertebrae.⁴⁰



Fig. 20.2 Apert syndrome. Typical facial (a) and hand (b) appearances.



Fig. 20.3 Pfeiffer syndrome. Typical hallux deformity.

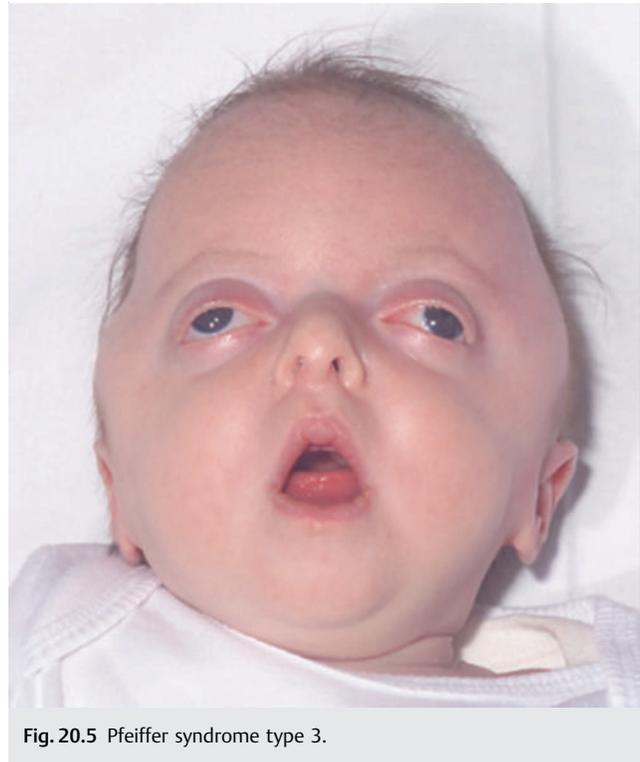


Fig. 20.5 Pfeiffer syndrome type 3.



Fig. 20.4 Pfeiffer syndrome type 1.

The difference between types 2 and 3 is that type 2 has the cloverleaf pattern of skull deformity (see below).

Neurocognitive development in types 2 and 3 Pfeiffer syndrome is usually delayed, although with active intervention aimed at improving the airway and reducing raised ICP, the outlook is not as dire as was once assumed.⁴¹

20.1.4 Cloverleaf Skull (Kleeblattschaedel) Deformity

Kleeblattschaedel anomaly, or cloverleaf skull, is the descriptive term given to a particularly severe form of synostosis-associated cranial deformity,⁴² one that poses a particular challenge for the craniofacial surgeon.^{43,44}

Although it usually occurs in association with Pfeiffer syndrome (of which it forms type 2), it can occasionally complicate Apert and Crouzon syndromes.

Cloverleaf skull is produced by a particular combination of suture fusions and raised ICP due to hydrocephalus. The sagittal and squamoparietal sutures are open, but a complex form of bicoronal synostosis results in a bony constriction band that runs posteriorly from the pterions to the lambdoids. When hydrocephalus is added to this bony pattern, the infant's skull expands upward (above) and laterally (below) the constriction band to produce a characteristic trefoil (cloverleaf) shape (► Fig. 20.6).^{38,45–47}

20.1.5 Saethre-Chatzen Syndrome

Saethre in 1931 and Chatzen in 1932 described an autosomal-dominant condition in which are combined with great



Fig. 20.6 Pfeiffer syndrome type 2. Cloverleaf pattern.

variability⁴⁸ features of coronal synostosis (uni- or bilateral), digital abnormalities that include short digits and partial syndactyly,⁴⁹ a low frontal hairline, a prominent nose, ptosis (► Fig. 20.7), and more rarely fusions of the cervical spine.⁵⁰

Complications like exorbitism and airway obstruction are uncommon, raised ICP is rarely of functional significance,⁵¹ and the neurocognitive outcome may be only modestly affected, if at all.⁴⁸

20.1.6 Muenke (*FGFR3* Mutation) Syndrome

This condition, one of the less severe of the craniofacial syndromes, is of interest because rather than being first described on the basis of the appearance of those affected, it was “discovered” during the explosion of knowledge about the genetic basis of the craniofacial syndromes that occurred during the 1990s.⁵²

Muenke syndrome has many manifestations,⁵³ but the synostosis typically affects either one or both coronal sutures.⁵⁴ Indeed, many patients previously diagnosed with isolated unicoronal craniosynostosis are now known to carry the *FGFR3* mutation.⁵⁵ Those with bicoronal synostosis typically have a broad and shallow supraorbital region with a protruding upper forehead (► Fig. 20.8).

Complications like raised ICP and airway obstruction are rare; however, although the development of a child with Muenke syndrome may be unaffected, a degree of learning difficulty is not uncommon.⁵²



Fig. 20.7 Saethre-Chotzen syndrome.

20.1.7 Craniofrontonasal Dysplasia

In this X-linked⁵⁶ syndrome (► Fig. 20.9), bicoronal synostosis (usually asymmetric in its effect) is associated with hypertelorism, wiry (“unruly”) hair, a prominent gap between the central incisors, a bifid nose,^{57–59} and sometimes abnormalities of the optic discs.⁶⁰ Development is usually unaffected, and treatment is indicated predominantly for cosmetic reasons.⁶¹

20.1.8 Carpenter Syndrome

This very rare condition⁶² is mentioned here for completeness because it is the only one of the craniofacial syndromes that has an autosomal-recessive pattern of inheritance. Also known as acrocephalopolysyndactyly because of the extra digits that form part of the clinical picture, the cranial deformity is due to various combinations of craniosynostosis.^{63,64}

20.2 The Molecular Genetics of Syndromic Craniosynostosis

With the exception of Carpenter syndrome (autosomal-recessive⁶⁵) and craniofrontonasal dysplasia (X-linked⁵⁶), the craniosynostosis-associated syndromes have an autosomal-dominant pattern of transmission. (For a summary linking the clinical

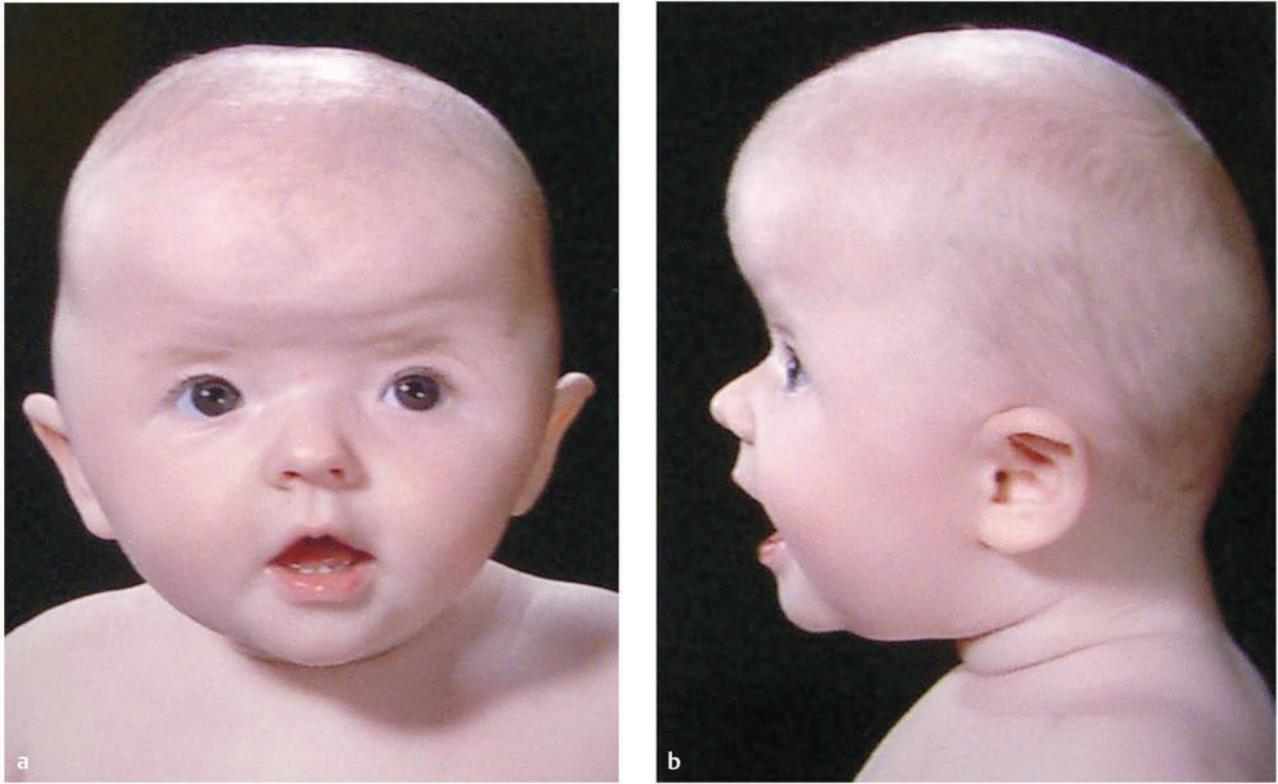


Fig. 20.8 (a,b) *FGFR3* mutation (Muenke syndrome).



Fig. 20.9 Craniofrontonasal dysplasia.

features of syndromic craniosynostosis to their underlying genetic abnormalities, see the review by Rice.¹)

The realization that many of the craniofacial syndromes are monogenetic (due to the mutation of a single gene) plus the investigation of families with several affected members led in the 1990s to an intense examination of the genes for a fibroblast growth factor group of tyrosine kinase receptors (FGFR I, FGFR II, and FGFR III) as candidate genes. These receptors are well preserved across a range of species and are involved (among many other activities) in cranial and limb development.^{66–69} It is now known that a particular position within each FGFR protein is strongly linked to craniosynostosis because mutations in their genes (*FGFR1*, *FGFR2*, and *FGFR3*) cause Pfeiffer, Apert, and Muenke syndromes, respectively.⁷⁰

Tyrosine kinase receptors straddle the cell membrane and have extracellular, transmembranous, and intracellular components. Mutations responsible for many of the craniosynostosis syndromes affect the extracellular component of FGFR II and act by provoking “gain of function”—the receptor overresponds either to its (appropriate) fibroblast growth factor (FGF) or to other (inappropriate) chemical signals.¹⁰

In contrast, mutation of the transcription factor *TWIST* gene (which is part of the FGFR signaling pathway and like the FGFs is expressed in calvarial bone⁷¹), which is responsible for Saethre-Chotzen syndrome, acts by causing functional loss.⁷²

At a molecular level, the situation is complicated by the functional diversity of the various *FGFR* mutations.⁶⁸ For example, there are a number of individual variations of (say)

Table 20.1 Genetic mutations responsible for the syndromes described in this chapter

GENE (CHROMOSOME)	RAB23 (6)	TWIST (7)	FGFR1 (8)	FGFR2 (10)	FGFR3 (4)	References
SYNDROME						
Apert				✓		74
Crouzon				✓		8,174,175
Crouzon with acanthosis nigricans					✓	18,75
Pfeiffer			✓	✓		8,9,75,176,177
Pfeiffer and Crouzon			✓			8
Saethre-Chotzen		✓				48
Muenke					✓	52
Carpenter	✓					65

*FGFR2*⁷³ responsible for what from a clinical perspective would be labeled Crouzon syndrome—approximately 30 have been identified to date. However, 95% of children with Apert syndrome have one of only two genetic variations on the extracellular portion of *FGFR II*.^{8,18,29,74} As already described, not only may Pfeiffer syndrome be associated with mutations in either *FGFR2* or *FGFR1*,^{9,75} but identical mutations in *FGFR2* can cause both Pfeiffer and Crouzon syndromes (► Table 20.1).⁸

Although confirmation of a particular mutation may not affect a child's immediate management, it does allow a more informed prognosis to be given to parents. Furthermore, the discovery of the *FGFR3* mutation in a child previously thought to have nonsyndromic unisutural synostosis, for example, will warn the craniofacial surgeon that a degree of relapse/reversion may occur following reconstructive surgery⁷⁶ (see below).

Knowledge of the responsible mutation also has important implications for genetic counseling. Parents who already have an affected child may wish to avail themselves of the opportunity not only for prenatal ultrasound examination of the fetus^{77–80} but also for preimplantation diagnosis when considering further pregnancies.^{81,82}

Research continues into the possibility of either gene substitution therapy following fetal diagnosis or a “vaccine” that interferes with *FGFR* function and could block some or all of a syndrome's most disabling features.⁸³

20.3 Principles of Surgical Management

It is essential that children with a craniofacial syndrome be referred to a suitably staffed unit as early as possible so that the correct diagnosis (both genetic and clinical) can be made, the risk for complications assessed, and a management plan tailored to each individual child's needs devised.

As the majority of craniofacial syndromes result from a mutation of a particular gene (usually of the *FGFR* series), it should be no surprise that such mutations continue to exert their ill effects for as long as the cranial and facial skeleton is growing. It

is this phenomenon that causes the anomalies corrected during reconstructive surgery to eventually drift toward their preoperative state despite what appeared at the time of surgery to have been a satisfactory result, even to the extent that repeated surgery is required.^{84,85} Wong et al wrote of their results of fronto-orbital surgery: “In the final analysis, the expression of the underlying genetic defect probably is the major determinant of the final fronto-orbital position despite our best surgical efforts.”⁸⁶ Or, as Kohan et al concluded in their report of twins with Pfeiffer syndrome (after each twin had received a different treatment strategy), “The genetic mutation may have overridden the different surgical interventions.”³⁹

The degree to which such reversion occurs (which is not to be confused with relapse due to the failure of bone grafts or plates and screws or any injurious effects of the procedure itself) is influenced by the severity of the gene's phenotypic expression and the age of the child when surgery is performed. Thus, reversion is seen most often in the severely affected child operated upon at a young age whose craniofacial growth is proceeding rapidly; it is less of an issue in a more mildly affected child whose growth is nearly complete⁸⁷ (and, of course, in those whose bicoronal synostosis (say) turns out to be nonsyndromic⁸⁸).

All this has important implications for the timing of surgery. If the result of a reconstructive procedure for a child with syndromic synostosis is to be stable into adulthood, it should ideally be postponed until the most active growth phase of the area being operated upon (e.g., the fronto-orbital region or the maxilla) has been completed *unless a particular functional complication demands earlier intervention*.^{89–91} This principle also holds good for the management of hypertelorism.⁹²

In practice, this means that the majority of children with Apert syndrome⁹³ and the more severe forms of Pfeiffer and Crouzon⁹³ and cloverleaf⁹⁴ syndromes may require several procedures during their early years to treat such functional issues as raised ICP, exorbitism, airway obstruction, and psychological issues related to their appearance (e.g., teasing).³⁵ In contrast, for more mildly affected children (e.g., with Saethre-Chotzen or Muenke syndrome⁷⁶), reversion is less of an issue, even after early surgery.

In brief, the complexity of decision making for children with syndromic craniosynostosis means that if they are to achieve their optimal developmental outcome, their management should be undertaken only in multidisciplinary units specializing in their care.^{51,91}

20.4 Functional Complications of Syndromic Craniosynostosis

20.4.1 Raised Intracranial Pressure

Raised ICP is a well-recognized complication of syndromic craniosynostosis.^{95,96} Its incidence is strongly related to the severity of the phenotype; raised ICP is unusual in Muenke and Saethre-Chotzen syndromes and nearly inevitable in Pfeiffer type 2 syndrome (cloverleaf skull deformity).

In a study of 49 children with Crouzon syndrome from our unit,⁹⁷ raised ICP occurred in 30. The predominant cause was craniocerebral disproportion in 17, hydrocephalus in 10, and airway obstruction in 3. It recurred in 14 of the 30 after successful treatment of the first episode, and 3 experienced a third episode. Those in whom raised ICP was first diagnosed before the age of 1 year were those in whom it was most likely to recur, although not necessarily for the same reason (e.g., the onset of hydrocephalus following a vault expansion for venous hypertension).

Marucci et al⁹⁸ studied our cases of Apert syndrome. Raised ICP first occurred at an average age of 18 months in 20 of 24 children. It was treated with vault-expanding surgery in 16, cerebrospinal fluid (CSF) diversion in 2, and relief of airway obstruction in 2. It recurred in 7 patients, on average 3 years and 4 months later.

Our experience of Pfeiffer syndrome shows a similar incidence of raised ICP requiring intervention as that in our children with Apert syndrome.⁹⁹

Raised ICP can be responsible for a progressive deterioration in vision that leads eventually to blindness.^{100,101} In one assessment of visual acuity in children with syndromic craniosynostosis, 40% had function in their better eye below a level (6/12) that would allow them to hold a driving license in the United Kingdom.¹⁰²

Whether raised ICP in syndromic craniosynostosis (in the absence of hydrocephalus) can affect cognitive development over and above the effects of other frequent complications, such as chronic airway obstruction, feeding difficulties, and failure to thrive, plus any direct effects of the mutated gene upon the brain itself, is debatable. Renier et al,^{34,95} as well as other investigators, have proposed such a connection, but it is always difficult to untangle the effects of raised ICP alone from those of other manifestations of a child's phenotype (e.g., how severely their breathing is affected). However, until more definite information becomes available, the neurosurgeon's default position must always be to assume that raised ICP left untreated can indeed impair developmental outcome.

The presence of increased ICP is suggested by:

- Clinically: bulging of still-open fontanelles; stretched sutures and craniectomy defects; in older children, headache and vomiting

- Radiologically: a generalized "beaten-copper" appearance on skull radiographs in the presence of multiple suture fusions¹⁰³; progressive ventriculomegaly and effacement of the cortical sulci on magnetic resonance (MR) images and/or computed tomographic (CT) scans¹⁰⁴
- Ophthalmologically: papilledema¹⁰⁵ with or without abnormal electrodiagnostic studies and a decrease in visual acuity¹⁰⁶⁻¹⁰⁸
- On invasive ICP monitoring, the "gold standard" for the assessment of ICP:^{95,96} It is important to recognize that the figures most often used to interpret the results of ICP monitoring in childhood (normal, < 10 mm Hg; borderline, 11 to 15 mm Hg; raised, > 15 mm Hg) are "best guesses" based on a variety of assumptions. (Understandably, the parents of healthy children are reluctant to subject them to an invasive procedure performed for essentially academic interest.)¹⁰⁹ Indeed, whether an ICP of 15 to 20 mm Hg can be responsible (in the absence of other problems) for any functional impairment is debatable.

It is important to remember that although the ICP may be normal when a child first presents, the dynamic nature of the syndromic craniosynostosis process means that ICP monitoring (which in our unit includes regular ophthalmic assessments) should continue until a child is at least 8 years old; our experience is that it is unusual for raised ICP to develop or recur at an age older than that.

Causes of Raised Intracranial Pressure in Syndromic Craniosynostosis

Although the four principal causes of raised ICP in children with syndromic craniosynostosis are considered separately here, some overlap is common. Indeed, they often interact to result in a vicious cycle (► Fig. 20.10); during active (rapid eye movement, or REM) sleep, airway obstruction and periods of apnea cause CO₂ retention, drops in SpO₂, and cerebral vasodilation that produce waves of very high pressure lasting 10 to 20 minutes superimposed upon a baseline that may be only moderately elevated (► Fig. 20.11). During these waves of high pressure (most obvious on overnight

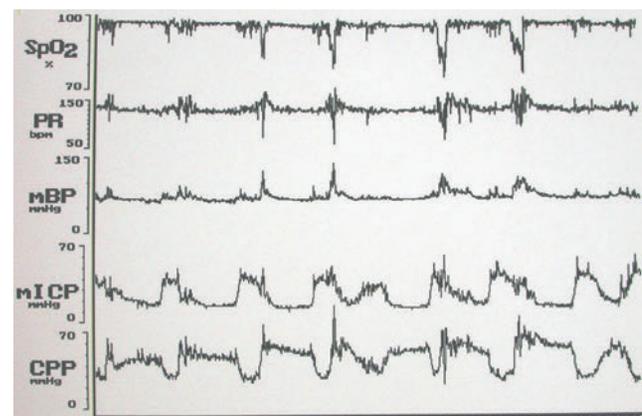


Fig. 20.10 Overnight record showing waves of elevated intracranial pressure associated with drops in SpO₂, elevations in blood pressure, fluctuations in pulse rate, and drops in cerebral perfusion pressure.

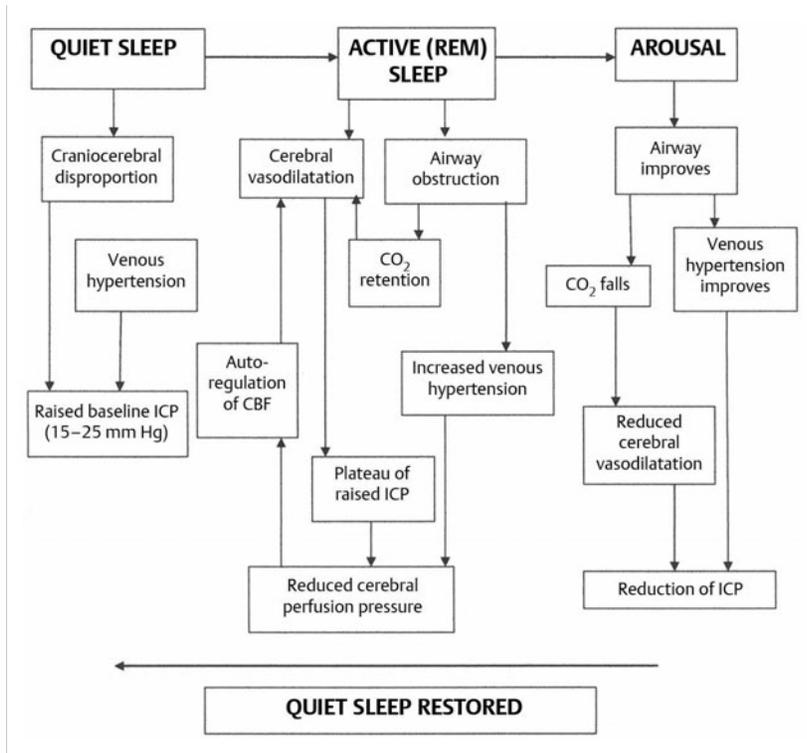


Fig. 20.11 The vicious cycle of raised intracranial pressure/airway obstruction/venous hypertension. CBF, cerebral blood flow; ICP, intracranial pressure; REM, rapid eye movement.

recordings), the cerebral perfusion pressure can fall to as low as 14 mm Hg.¹¹⁰

Craniocerebral Disproportion

Intracranial volume (ICV) can conveniently be measured with CT data¹¹¹ in children with¹¹² (and without¹¹³) craniosynostosis, but it has proved an unreliable predictor of raised ICP.^{114,115}

Although it was once thought that the cause of raised ICP in syndromic synostosis was restraint of the growing brain by a skull that could not adequately accommodate it, it is now recognized that this is a relatively unusual situation. Indeed, in Apert syndrome, the ICV, although normal at birth, may actually be greater than normal by the time raised ICP appears.^{113,116} Fortunately, the various forms of vault expansion surgery originally designed to increase ICV are equally effective in reducing raised ICP with a more common cause—venous hypertension (see below).

Airway Obstruction

Impairment of the upper airway is common in the severely affected child with syndromic synostosis and is an important contributor to the vicious cycle that determines ICP in these children (see Fig 20.9).¹¹⁷ The peaks of ICP that can reduce cerebral perfusion pressure to as low as 14 mm Hg are invariably associated with episodes of airway obstruction during REM sleep. The practical importance of this is that improvement in the airway (e.g., by adenotonsillectomy,¹¹⁸ a nasopharyngeal prong, or tracheostomy) may help control ICP.

Hydrocephalus and Chiari 1 Deformity

As many as 40% of children with syndromic synostosis have a degree of ventricular enlargement,¹⁰⁴ but in many it is

nonprogressive. It is important, therefore, that the craniofacial surgeon does not proceed to treatment—a shunt insertion, for example—unless ventriculomegaly is progressive and other indicators of raised ICP are present.

Hydrocephalus occurs particularly when there is constriction of the skull base and early closure of the lambdoid sutures, which explains why it occurs more frequently in Crouzon and Pfeiffer (types 2 and 3) syndromes than in Apert syndrome.¹¹⁹

Although the fourth ventricle is usually small compared with the third, our experience (and that of others¹²⁰) of endoscopic third ventriculostomy has not been encouraging, and we prefer to insert a ventriculoperitoneal shunt, particularly in a young child with very high pressure.

Constriction of the skull base, hydrocephalus and raised ICP, and herniation of the cerebellar tonsils (the Chiari 1 deformity) are linked in a cycle of cause and effect.^{119,121} The Chiari 1 deformity is seen most often in children with a constricted skull base, and although its progression (with additional buckling of the lower brainstem) is facilitated by raised ICP, it is also a risk factor for the development of hydrocephalus.¹²²

When tonsillar herniation and brainstem distortion in a child with syndromic synostosis become symptomatic (usually when respiratory studies suggest a central as well as an obstructive contribution to breathing problems¹²³; see below), a foramen magnum decompression may be needed.

Raised Venous Pressure

Intracranial venous hypertension is a major contributor to raised ICP in children with syndromic synostosis.¹²⁴ Its cause is narrowing or actual occlusion of venous channels through the skull base¹²⁵ that impedes the outflow of blood from the cranial compartment. The rise in venous pressure thus produced is aggravated by airway obstruction, and by interfering

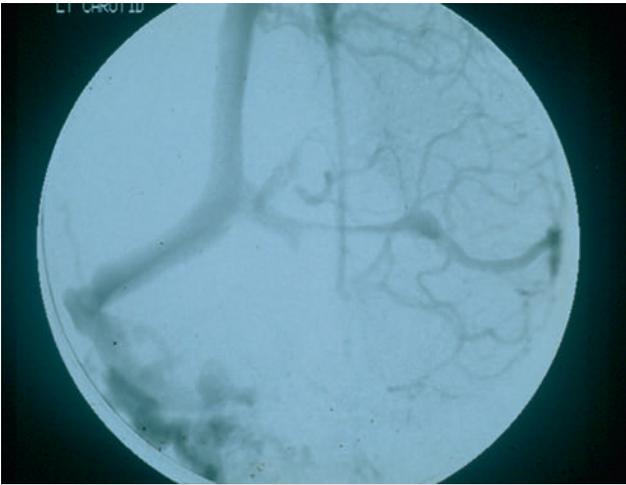


Fig. 20.12 Digital subtraction angiogram of a child with syndromic craniosynostosis showing near-occlusion of the left transverse sinus, absence of both sigmoid/jugular complexes, and a mesh of collateral veins palpable in the right retromastoid region.

with CSF absorption, it is also a potential contributor to hydrocephalus—a situation similar to that often seen in achondroplasia.¹²⁶

In a digital subtraction angiography study of 23 of our children with syndromic synostosis and raised ICP,¹²⁷ 18 had either complete or more than 50% occlusion of the sigmoid/jugular complex on one or both sides (► Fig. 20.12). Extensive collaterals through the retromastoid region and other transosseous channels can cause troublesome bleeding during reflection of the extensive skin flaps often required for craniofacial surgery.^{44,128}

Treatment would ideally either open up or bypass the obstructed venous channels. Although this has not proved successful,¹²⁹ any vault-expanding procedure will lower ICP due to venous hypertension—another example of the close relationship among the various causes of raised ICP in syndromic synostosis.

In summary, raised ICP does not develop in all children with syndromic synostosis (about 40% of our children with Crouzon syndrome and only one-third of those in Renier's series had an ICP above 15 mm Hg⁹⁵), and not all who do are best treated by cranial vault expansion. This raises questions about the policy of many craniofacial units—the routine use of the fronto-orbital advance when these children first present.

20.4.2 Airway Obstruction

Impaired respiratory function, particularly at night, when snoring is a frequent complaint, is a common problem for the more severely affected child with syndromic craniosynostosis. It is usually caused by airway obstruction due to narrowed nares, cramped nasal passages, a maxilla constricted in all planes, and tracheal softening; however, a central component occurs when there is brainstem compression from a Chiari 1 deformity.¹²³ An airway clear at birth may become obstructed during later growth of tonsillar and (in particular) adenoidal tissue in the restricted space available.

In addition to contributing to raised ICP, breathing difficulties impair the ability of the infant and young child to feed and are an important contributor to their failure to thrive. In older children, disturbed nights lead to sleepiness during the day and can interfere with schooling.

All children in whom breathing difficulties are suspected should undergo an overnight respiratory sleep study. Although the most common cause is upper airway obstruction, such a study will determine whether a central component is present; if there is a central component and it is associated with a Chiari 1 deformity, a foramen magnum decompression may be required.¹²³

Management involves (in ascending order of magnitude) the following: insertion of a nasopharyngeal airway,¹³⁰ adenotonsillectomy (which may need to be repeated as the child grows),¹¹⁸ continuous positive airway pressure (CPAP),^{131,132} tracheostomy, and finally operations that open the airway by advancing the maxilla—the Le Fort III advance (performed at an average age of 8 years in Fearon's series¹³³) and the monobloc frontofacial advance¹³⁴ with or without distraction—and widening it (the facial bipartition).

20.4.3 Corneal Exposure

Recession of the maxilla below and the fronto-orbital region above can leave the corneas exposed and in danger of permanent scarring.

Temporary measures to protect them include the instillation of lubricating drops (particularly useful when the eyes do not close completely at night) and tarsorrhaphy, although this can raise the intraocular pressure in the face of severe exorbitism. Longer-term protection requires advancement of the bony orbital rim, either in part with a fronto-orbital advance or completely with a fronto-orbital advance combined with a Le Fort III maxillary advance or a frontofacial monobloc procedure (which can in exceptional circumstances be performed as a semi-emergency procedure¹³⁵).

20.4.4 Cosmesis

The cosmetic disabilities that most trouble patients with syndromic synostosis and their families include a misshapen forehead, protruding eyes, eyes set too far apart (hypertelorism), and an upper jaw that is set back while the lower jaw protrudes.

In correcting for cosmesis alone, it is important to bear in mind the caveat already presented—that surgery carried out on a part of the craniofacial skeleton that is still growing may need to be repeated either wholly or in part in order to achieve a result that will prove stable over time. Each of the various components of the craniofacial skeleton has its own growth pattern. Waitzman et al have calculated that the cranio-orbito-zygomatic skeleton reaches more than 85% of its adult size by the age of 5 years.^{136,137} Our own policy, based more on clinical observation than on measurement, is to assume that a forehead and supraorbital region in a satisfactory configuration at around 10 years of age are unlikely to need further correction, and that cosmetic reconstructions after that age can focus more on the maxilla and mandible, where

growth will continue until secondary dentition is complete during the mid to late teens.

20.5 Craniofacial Operations for the Child with Syndromic Craniosynostosis

Paul Tessier, who was a plastic surgeon, was the first to combine the skills of the plastic surgeon and those of the neurosurgeon to create what we recognize today as the specialty of craniofacial surgery.^{138,139} Indeed, all the procedures to be described here, if not actually designed by him, were introduced with his approval and incorporated into his extensive surgical repertoire.

20.5.1 General Points

Although strictly outside the scope of this chapter, the following points should always be considered before a child with a craniosynostosis-associated syndrome is taken to surgery.

Anesthesia

Craniofacial surgery should never be undertaken without the input of pediatric anesthesiologists experienced in the pre-, intra- and postoperative care of children who may already have an obstructed airway and raised ICP, and who (because of anomalous cranial venous drainage¹⁴⁰) may be at risk for major hemorrhage during the procedure.¹⁴¹

An example of their preoperative role is providing input regarding the decision of whether a child with an obstructed airway who is about to undergo major frontofacial surgery should first have a tracheostomy.

General anesthesia for a patient with a severe facial deformity may also call for fiberoptic intubation, an essential skill for the craniofacial anesthesiologist.

The circulating blood volume of a young child is small, and losses that an older patient can withstand can lead to a swift circulatory collapse. A fail-safe approach is always to be ahead rather than behind concerning blood loss. Large-volume transfusions (one volume of circulating blood or more) will interfere with coagulation, and immediate access to fresh frozen plasma, platelets, and other clotting factors is essential.

Other ways of reducing the need for transfusion—or for the number of donors to whom the child is exposed—include the preoperative use of iron supplements (to ensure the child comes to surgery with an optimum haemoglobin level), the (still controversial) prescription of EPO (erythropoetin), and (during surgery itself) the use of cell-savers and antifibrinolytics.

Correct positioning of the patient is vital in craniofacial operations, and the anesthesiologist plays an important role in this. A head-up tilt with no obstruction of the neck veins is essential to reduce intracranial venous hypertension, although such a position will expose the patient to a (in our experience) small risk for air embolism. When surgery is performed with the patient prone, great care must be taken to protect the often protruding eyes and avoid any abdominal compression that may impede venous return.

Incision

Access

Access to large areas of the skull and face is often required in craniofacial surgery. We favor a bicoronal incision whose center lies just behind the hairline and then falls in a gentle curve to behind each ear. This provides access to the entire skull and, thanks to the pliant skin of the young, also to the upper reaches of the face. The hair need only be braided and can be left unshaved.¹⁴² Unless dissection to the zygomatic arch through the layers of temporalis fascia is required, the temporalis muscle is elevated with the skin flap. There is then no need to resuspend it at the end of surgery, and the frontal branch of the facial nerve is protected.

Cosmesis

A scar on the head is best hidden if the hair lies across it rather than being parted by it—as happens with the “classic” neurosurgical bicoronal incision, which follows the line of the coronal sutures downward to the front of the ear. Many units employ a zigzag incision to provide both hair cover and the degree of skin stretch often needed when the skull vault has been expanded.

Infiltration

For many years, we have injected a large volume of a “tumescent” solution containing two types of local anesthetic, a steroid, adrenalin, and hyalase into the proposed incision, the skin flaps, and when indicated, the tissues of the face. We have found that this reduces postoperative swelling and also shortened hospital stay.¹⁴³

Complications

Of particular importance to the craniofacial surgeon are the following.

Cerebrospinal Fluid Leaks

Dural tears are likely to occur during craniofacial operations when there has been previous surgery (particularly if metallic plates and screws have had time to migrate inward¹⁴⁴) and when the skull base is very constricted. Osteotomy cuts through the anterior skull base place the frontal extradural compartment in communication with the (bacterially contaminated) nose, allowing CSF leakage that presents as rhinorrhea. The patient is then at risk for meningitis, and contamination of the extradural space can lead to infection of the often devascularized surrounding bone.

Measures to reduce the risk for CSF leakage complicating monobloc and similar procedures include (in addition to previous experience¹⁴⁵) the following: prophylactic placement of a lumbar drain at the start or end of the operation, placement of the skull base osteotomy no farther posteriorly than the foramen cecum, careful attention to the closure of any dural tears, covering the gap in the anterior skull base before the frontal bone is replaced with a vascularized pericranial flap, and finally the use of tissue adhesive to seal the area.

Fortunately, most CSF leaks cease spontaneously. Those that show no sign of settling over a day or so should be treated by the insertion of a lumbar drain. Leaks that persist (or recur) despite this may require a formal skull base repair, either transcranially or transnasally.

Infection and the Dead Space

The monobloc procedure by definition places the frontal extradural space and the nasal cavity in communication, something that a separation of the surgical components into a fronto-orbital advance and a Le Fort III advance does not do. However, any operation that increases the ICP carries the risk of leaving an air, blood, and serous fluid-filled dead space,¹⁴⁶ which together with the often devascularized bone surrounding it provides an excellent substrate for bacterial growth.

Discussion with the hospital's microbiologists is obligatory, both to determine the most suitable antibiotic regime to be used both prophylactically and to decide when infection is either confirmed or assumed in the absence of an obvious source.

In our unit, we have a low threshold for reopening the skin incision and thoroughly washing the surgical field with an antibacterial solution if infection is suspected.

Bone Defects

Cranial vault expansion often leaves areas of bone defect that in a child older than 1 or 2¹⁴⁷ years of age are unlikely to fill in spontaneously. We regularly use a "salami" of milled bone fragments that are mixed with tissue adhesive and then "rolled out" in a thin strip to provide permanent bone cover for such defects.¹⁴⁸

For the elective closure of bone defects in the older child we use when possible split calvarial bone.¹⁴⁹

Bone Fixation

The tendency of metallic plates and screws to migrate inward¹⁴⁴ has led us to avoid their use when possible, particularly in young children in whom sufficiently rigid fixation can usually be obtained with absorbable sutures. Metal plates and screws complicate subsequent operations when they become buried in bone; they sometimes eventually penetrate the dura and make tears that are difficult to repair inevitable during subsequent operations.

20.5.2 Craniofacial Procedures

The operations involved in the management of children with craniosynostosis syndromes cross many surgical specialties. Described here are those that include a neurosurgical element wholly or in part.

Fronto-orbital Advance

The operation most frequently performed in the management of syndromic synostosis is the fronto-orbital advance, in which the frontal bone and the supraorbital ridge are brought forward a couple of centimeters or so and then fixed in their

new position. The fronto-orbital advance both expands the intracranial volume and provides cover for the upper parts of the globes. Its cosmetic effect may be all that is required in the management of less severely affected children—some with Muenke or Saethre-Chotzen syndrome, for example. At one time, it was believed that the skull base osteotomies involved would "free" the facial skeleton from the skull base, allowing the maxilla to assume a more normal trajectory—the so-called "floating forehead."¹⁵⁰ However, as discussed earlier, it is now recognized that maxillary (and fronto-orbital) growth is determined more by the patient's genotype than by the effects of any frontal and base-of-skull disconnection.^{39,86}

When both coronal synostosis and maxillary hypoplasia require attention (as in the Crouzon, Apert, and Pfeiffer syndromes), the fronto-orbital advance can be combined with a Le Fort III⁸⁹ to advance the whole frontomaxillary complex as an alternative to the monobloc procedure.

Cranial Vault Expansion

The cranial vault is expanded anteriorly as a result of both the fronto-orbital advance (see above) and the monobloc procedure. However, biparietal and posterior vault expansions are also useful ways of lowering ICP due to craniocerebral disproportion with or without venous hypertension. A posterior expansion can when necessary be taken as far down as the foramen magnum to decompress a symptomatic Chiari 1 malformation. The released parietal bones or posterior vault can be left to float freely, but a greater increase in ICP is achieved if the bones are secured in their expanded position with bone struts and absorbable sutures. The degree of expansion achievable is limited by how far the overlying skin will stretch to accommodate the expansion, although such maneuvers as "relaxing" incisions in the galea and the use of looped tension sutures can ease edge approximation. The use of springs and distraction, however (see below), addresses this issue.

A cranial vault expansion may have unintended consequences, not the least of which is the conversion of a previously large but stable ventricular size into overt hydrocephalus.¹⁵¹

Springs Technology

The use of springs to move mobilized segments of the skull into a new position was introduced into craniofacial practice by Lauritzen et al.^{152,153}

We have also found springs a convenient way of providing a greater degree of vault expansion because of their gradual as opposed to immediate intraoperative stretching of the overlying skin (► Fig. 20.13). The scale of the surgery required to insert them is often less than that of a conventional vault expansion, but another operation to remove them once bone consolidation has been achieved is usually required.

Distraction Technology

Distraction provides another mechanism for moving bone gradually over days rather than immediately during surgery. The distractors are applied after the bone cuts have been

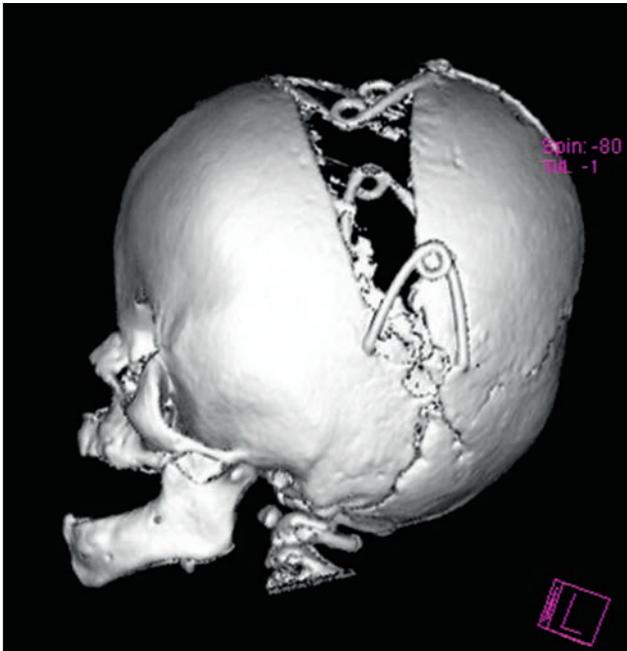


Fig. 20.13 A posterior vault expansion in a child with Apert syndrome performed with our unit's springs technology. (Image provided courtesy of Mr. Owase Jeelani, FRCS.)

made. The incision is closed, and then the mobilized bone segment is pulled (or pushed) a millimeter or so a day until it reaches its intended position. The distractors are retained until bone healing (consolidation) is complete¹⁵⁴ and then removed.

In craniofacial surgery, distractors have been used for fronto-orbital advances, cranial vault expansions, Le Fort III advances, and frontofacial monobloc procedures (with or without facial bipartition), in which they have been shown to provide a larger advance in terms of bone movement compared with previous techniques using immediate fixation.^{133,155–157} They are also used in stand-alone procedures to lengthen both the maxillary alveolus (Le Fort I) and the mandible.¹⁵⁸

Distractors fall into two groups—"internal" and "external." Internal distractors are effectively "ram screw" devices whose base plates are fixed to each side of the bone cuts. When the shaft of the distractor is rotated, the mobilized segment is pushed forward or backward.^{157,159} External distractors pull rather than push the mobilized bone segment. Wires attached to plates screwed to the (mobilized) bone are brought out through the skin and connected to a frame fixed by pins to the patient's head (► Fig. 20.14a,b). The frame is so constructed that it can be slowly expanded, a process that gradually pulls the bone forward. Again, once the desired amount of movement has been achieved, the wires and frame are left in position until bone consolidation¹⁵⁴ has been achieved.^{133,156}



Fig. 20.14 (a) External distraction with use of the RED (rigid external distraction frame; KLS Martin, Jacksonville, FL) system (b) to advance the monobloc segment in a child with progressive corneal exposure and airway obstruction due to Pfeiffer syndrome type 3.

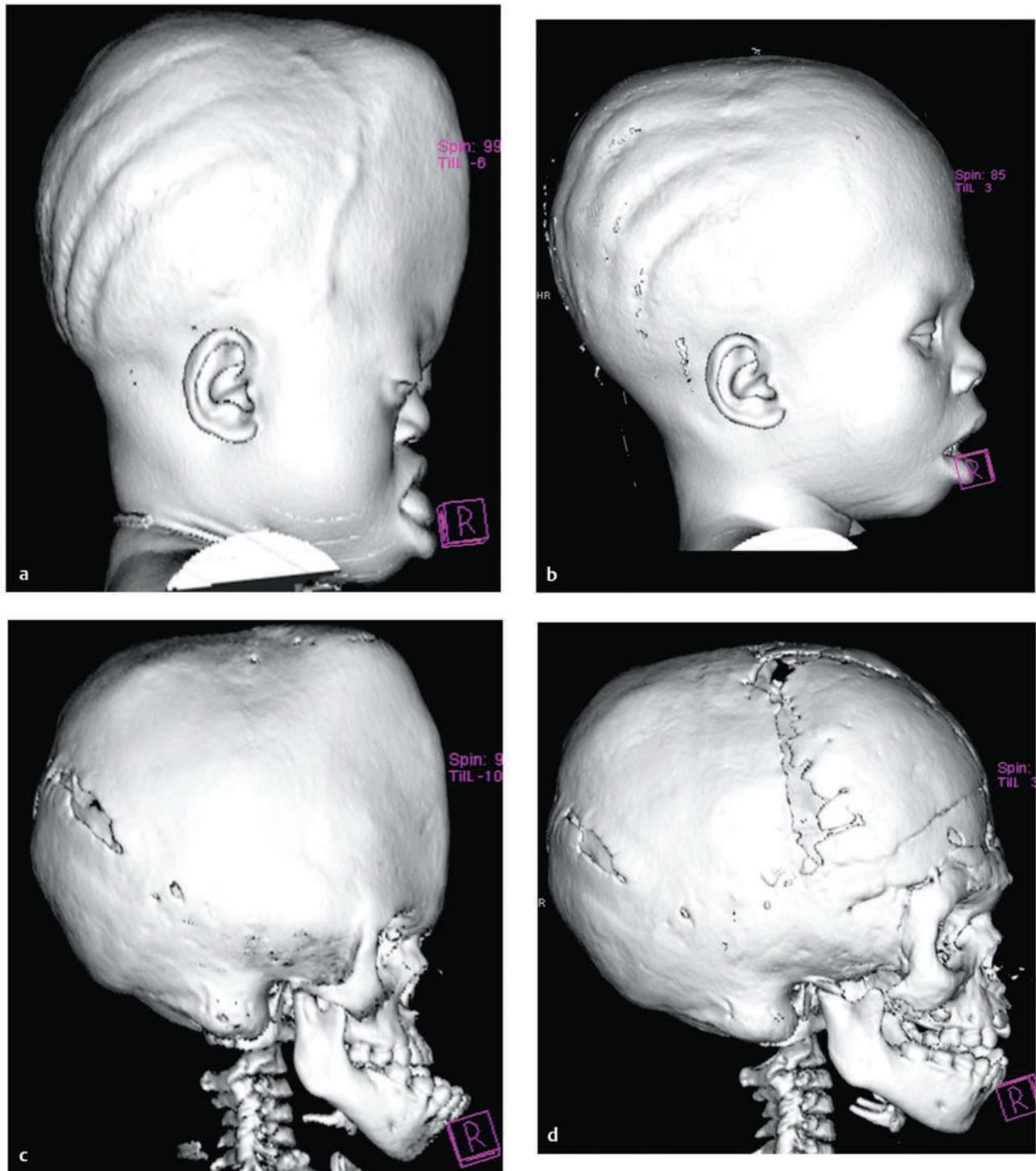


Fig. 20.15 Three-dimensional reconstructions showing appearances (a,b) before and (b,d) after monobloc frontofacial advance by distraction in a child with Crouzon syndrome who underwent previous posterior vault expansion surgery.

Monobloc Frontofacial Advance

The monobloc frontofacial advance, pioneered by Ortiz-Monasterio et al¹⁶⁰ and refined by Molina,¹⁶¹ has in many units become the preferred procedure for the management of patients with complex frontofacial deformities due to syndromic craniosynostosis. It expands the ICV, provides circumferential bony cover for exposed eyes, and can open up a constricted oro- and nasopharynx.¹³⁴

The combined fronto-orbital and maxillary complex is mobilized, advanced, and then maintained in its new position with bone grafts.¹⁶² In the early experience in our unit with its use in children younger than 3 years, the high incidence of complications, including infection and CSF leakage,¹⁶³ led us to confine its use to older patients—those approaching the end of facial growth, for example.

The advent of distraction technology, however, allowed us to reassess the monobloc,¹³⁴ and although it remains a very major procedure with arguments for and against,¹⁶⁴ we (and others¹⁶⁵⁻¹⁶⁷) now deploy it even in children younger than 3 years, but only if their combination of airway obstruction, corneal exposure, and raised ICP is severe enough to justify such a major operation in such young children (► Fig. 20.14a,b and ► Fig. 20.15a–d).

Bradley et al¹⁴⁵ have provided an account of how combining the monobloc with distraction can lead to a fall in the complication rate (in particular CSF leaks). The addition of neuro-navigation to the operation has the potential to make safer the effectively “blind” osteotomy cuts through the pterygoids necessary to separate the maxilla from the skull base.¹⁶⁸

Although in theory the advance of the whole orbital circumference risks moving the globe with it, this has not proved a practical disadvantage,¹⁶⁹ and our experience has been that the monobloc has cosmetic advantages¹³⁴ over the combined fronto-orbital advance and Le Fort III procedure, which has a tendency to overlengthen the face.

Facial Bipartition

Hypertelorism has for many years been treated with a “box” osteotomy, in which the anterior rim of each orbit is mobilized, a piece of bone of the required width is removed from between them and excised, and the two orbits are then approximated and fixed in their new position.⁹² The procedure

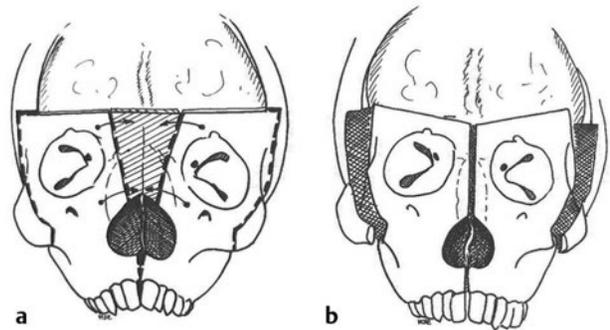


Fig. 20.16 Diagrammatic representation of the facial bipartition before (left) and after (right) closure of the V.



Fig. 20.17 A child with Apert syndrome (a) before and (b) after the use of distraction for facial bipartition.

does not alter the configuration of the maxilla, which so often is in need of attention in syndromic craniosynostosis, and the infraorbital bone cuts risk damage to the buds of the upper teeth.⁶¹

To overcome these issues, Van der Meulen¹⁷⁰ proposed the facial bipartition. The operation starts with mobilization of the frontofacial segment, as in a monobloc, but then a V-shaped piece of bone is cut from the frontonasal region, the apex of the V being at the level of the (often high-arched) hard palate. A vertical cut below this turns the V into a Y. Closure of the V brings the orbits closer together¹⁷¹ and expands the maxilla¹⁶² (► Fig. 20.16). This corrects any downward slant of the eyes and also bends the face in a convexity and forward in the horizontal plane, which makes it particularly effective for the child with Apert syndrome whose facial deformity includes hypertelorism combined with midface recession in both the horizontal and vertical planes.¹⁷²

As with the monobloc, the bipartitioned segment can, if required, be moved forward with distraction¹⁷³ (► Fig. 20.17).

20.6 Summary

The discovery of many of the gene mutations responsible for the craniosynostosis-associated syndromes has provided an explanation for what specialists in this area had observed for many years—that these conditions represent a dynamic rather than a static process.

Effective management requires a team of suitably experienced specialists who can tailor management to the needs of the individual child.

Mildly affected children can undergo primarily cosmetic procedures at a young age in the expectation that they may not need to be repeated.

For severely affected children, however, early management is concentrated upon the various complications that can prevent them from achieving their full developmental potential. These include in particular upper airway obstruction, corneal exposure, and raised ICP.

If stable long-term cosmetic results are to be achieved, final reconstruction may need to be postponed until the cessation of growth of the affected areas—the late teenage years—and the establishment of adult dentition in the case of the maxilla.

Pearls

- The craniosynostosis-associated syndromes are dynamic as opposed to static phenomena.
- The gene mutations responsible for them continue to exert their effects as long as growth continues.
- The incidence of complications such as raised ICP is strongly correlated to the particular syndrome (e.g., high in Pfeiffer syndrome, low in Muenke syndrome) and the severity of its expression.
- The more severe the phenotype, the more likely it is that the anomalies corrected in early reconstructive surgery will revert to their preoperative status.
- Affected children (and adults) should be managed only in units where a multidisciplinary team of experienced specialists is available.

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21 Craniopagus Twins

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Craniopagus is among the rarest and most complex congenital abnormalities, with a history detailed in both mythology and contemporary medical literature. The technical ability to separate craniopagus twins did not develop until 1952, and even then only one twin survived the operation. Overall outcomes have been mixed until recently, with one twin of the pair usually experiencing severe neurologic consequences and often death after separation. Although modern neurosurgical techniques have evolved, the separation of craniopagus twins continues to be one of the most challenging and risky procedures in neurosurgery. With the historical record full of surgical misadventures, the decision to separate craniopagus twins poses not only a complex surgical dilemma but rightfully an ethical and philosophical challenge, as well. As additional cases have come to medical attention, two opposing strategies for separation have emerged. As the name implies, single-stage separation involves a single marathon surgery during which physical separation is performed, although preparatory surgeries to expand the scalp may precede the separation. In the last two decades, a new strategy involving multiple-stage separation has developed. In staged separations, multiple craniotomies spread over a period of several months gradually eliminate the venous and tissue connections to permit each child to develop independent cerebral venous drainage. Both single-stage and multiple-stage separation attempts have been vocally advocated as superior, but recent cases have demonstrated improved survival and outcomes with a multiple-stage approach. In this chapter, we provide a historical and epidemiologic perspective on this condition, illustrate strategies for presurgical evaluation, discuss the techniques for separation, with an emphasis on the rationale for the multiple-stage approach, and share examples of cases deemed nonseparable with current techniques and technology. We also briefly discuss the socioeconomic impact of taking on one of these challenging cases and the ethical dilemma raised by the huge allocation of resources needed to undertake a successful separation attempt.

21.1 Craniopagus: Brief Historical Perspective

Notable recent cases and attempted separations have become worldwide spectacles, leveraging our innate curiosity about these individuals and showcasing the most difficult of neurosurgical procedures; however, the same curiosity is manifested in literature and art dating to antiquity. As in the present day, those who survived infancy became the subject of fascination for some and were feared, ridiculed, or exploited by others. The earliest documented case of craniopagus twins dates from the 15th century (► Fig. 21.1). These twins were born in Bavaria, Germany, in 1491 and were described as a *monestare* (“warning from God”).¹ In a famous case of craniopagus parasiticus in the 1770s, the twins were known as the boys of Bengal² (► Fig. 21.2). In the early 17th century, it became quite popular to place conjoined twins on exhibit in traveling road shows and circuses as “freaks” of

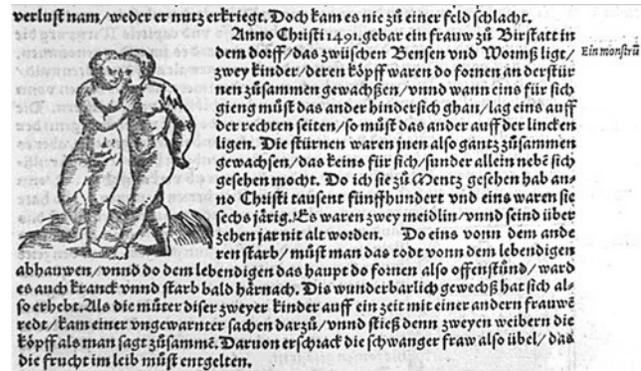


Fig. 21.1 Early image of conjoined twins. (From *Cosmographia*, by Sebastian Münster (1488–1552), a Basel edition printed by Sebastian Heinrich-Petric in 1550 (see leaves dclxxvii–dcccivii, i.e. 767–768). From the personal collection of J.T.G.)



Fig. 21.2 Preserved skull of the boys of Bengal. (From the Hunterian Collection.)



Fig. 21.3 The McCarter twins. Photos such as these were given out at events and affairs. The image at the lower left includes information about the press agent. (Images from the personal collection of J.T.G.)

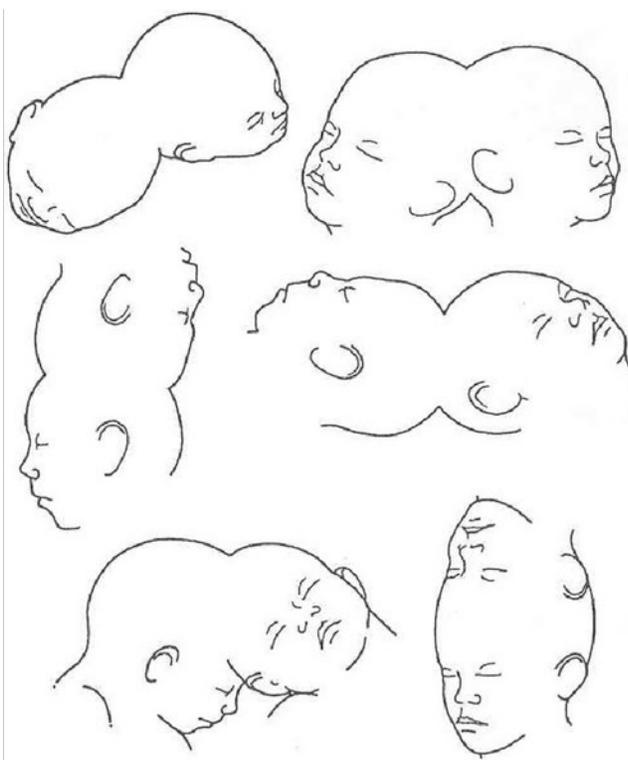


Fig. 21.4 Drawing showing variations on the union in craniopagus twins. (Reproduced from Spencer R. Conjoined Twins: Developmental Malformations and Clinical Implications. Baltimore, MD: Johns Hopkins University Press; 2003.¹⁰)

nature. The showmen would also produce and distribute show cards and autographed pictures, thereby generating an extra and significant source of income (► Fig. 21.3). Even in the early medical literature, conjoined twins were described as “double monstrosities.”³

Several sets of craniopagus twins have lived into adulthood, although 75% die in the perinatal period and more than 90% have died by the age of 10 years, regardless of attempts at surgical separation.⁴ The first successful craniopagus surgery in which one twin lived was in 1952–1953. Oscar Sugar, MD, and his team in Chicago undertook the separation of Roger and Rodney Brodie.^{5,6} Although Roger died 1 month after surgery, Rodney lived to the age of 11 and died of complications of hydrocephalus. The first reported case in which both twins survived was reported just a few years later, in 1957.⁷ Christine Quigley highlights the history of several cases of craniopagus twins in her book entitled *Conjoined Twins*.⁸

21.2 Classification and Demographics of Craniopagus

In 1865, Forster⁹ introduced the term *craniopagus* to define twins joined by a union of the calvaria only¹⁰ (► Fig. 21.4). The union of the cranial vault is rarely symmetric and may involve any location on the head, leading to an infinite variation of configurations. This complexity is further complicated by variations in the degree of conjoining or sharing of underlying structures like the meninges, venous sinuses, and cortex, making each case surgically unique (i.e., no two cases are ever equivalent).

Despite of the variation, several authors have attempted to classify the phenotypic archetypes seen in craniopagus. O'Connell was among the first to attempt a classification schema, describing partial craniopagus, in which a limited surface area is affected, with intact or minimal cranial defects, and total craniopagus, in which an extensive surface area is shared, with widely connected cranial cavities. O'Connell further subclassified "vertical" craniopagus ("parietal craniopagus" according to the classification of Buchholz et al.¹¹) into types 1 through 3 based on the degree of cranial rotation. More recently, Stone and Goodrich augmented the partial and total divisions described by O'Connell, defining two additional main subtypes, angular and vertical, to describe the longitudinal angle of connection, regardless of axial rotation, and the facial rotation.⁴ They suggested that this classification might be used to better predict surgical outcomes based on the complexity of the various vascular interconnections.

Craniopagus is extremely rare, occurring once in every 0.6 to 2.5 million live births.^{4,12} The causal factor(s) that lead to craniopagus remain(s) unclear, with various embryologic theories proposed for both "incomplete fission" and "fusion" types.^{10,13} Although incomplete fission of a fertilized ovum was initially presumed to be the cause of conjoined twins, more current understanding of embryology suggests that the fusion of identical twin embryos during early development is likely the cause. There are no known environmental or genetic factors. The female-to-male ratio is nearly 4:1, but for this, too, no correlative or causal factors are known.

We have previously reported an extensive review of the literature from 1919 through 2006, which noted 64 well-documented cases of craniopagus, with 41 separation attempts. Of these, 29 were performed as a single-stage separation, and 12 separations were attempted with a multiple-stage approach.¹⁴

21.3 Risk Stratification of Separation

There are many reports of intra- and extraoperative misadventures; the decision to separate craniopagus twins is one that should be undertaken with serious deliberation and forethought. Until relatively recently, the decision to separate craniopagus twins inherently led to the sacrifice of one of the twins so that the other could live more "normally." Contemporary management has evolved to the point that a separation attempt is typically offered only if there is a hope of a reasonable outcome for both twins or if the life of one or both of the twins is in danger. As technology and our understanding of the complex craniopagus anatomy has grown, it is now recognized that the presence of shared dural venous sinuses is among the most challenging issues faced in any separation attempt. Equally important is a broad understanding of the numerous other risk factors that must be assessed in an evaluation of craniopagus twins for separation. As we have discussed in other publications,¹⁶ some of the factors critical to the surgical decision making are an understanding of the degree of shared scalp, calvaria, and dura (independent dural envelopes or incomplete dural separation, also called circumferential sinus lakes), the amount of separation/interdigitation or fusion of cortex or deeper structures, the extent of shared arterial connections/cross-flow and

common venous sinuses/drainage, and the presence of paired or separate venous outflow/drainage and ventricular systems.¹⁶ We have previously proposed a scheme similar to other neurosurgical risk stratification scales (e.g., the Spetzler-Martin scale for arteriovenous malformations) by which individual cases can be evaluated to determine the surgical risk (► Table 21.1).¹⁶ Our scheme assigns point values to provide a preliminary understanding of the degree of risk associated with attempted separation; a higher score is indicative of a more difficult separation. Few will debate the benefit or detriment of separation if the surgical risk is low or high, respectively, but the decision becomes more difficult in cases that fall between the extremes; however, this scheme may help with the evaluation.¹⁷ Although not fully validated, the proposed grading scale attempts to account for the most critical variables that experience has shown to influence outcome during the perioperative period, in an effort to add objectivity to a very subjective decision. Refinement, application, and validation of the scale will occur as additional cases come to modern neurosurgical evaluation.

21.4 Preoperative Assessment

Understanding and planning for the unique anatomy present in craniopagus is one of the most important factors that lead to a successful separation attempt. Equally important, a high-quality preoperative evaluation can determine which patients are truly inoperable. In the current state, preoperative evaluation consists of clinical monitoring, imaging, and anatomical modeling. Beyond the typical neurosurgical considerations are unique physiologic perturbations that occur in craniopagus that mandate cardiac, pulmonary, and renal management plans. These children often arrive in both cardiac and renal failure and can be severely ill. It has been our experience that the metabolic differences (renal, cardiac, pulmonary, other) between the twins can be quite extreme. These systems and their function can and will change during the perioperative period, and an experienced multidisciplinary medical team is necessary to take these patients up to and through a surgical separation safely. Given the complexity of the procedures and the potential for blood loss with each operation, separations must be delayed until after the patients reach an age and body weight that will allow them to tolerate significant blood loss.

Our ability to obtain high-resolution imaging and newer techniques for modeling blood flow have revolutionized the assessment of craniopagus twins. The reconstruction of high-resolution imaging accurately demonstrates critical neural and vascular structures. Post-processing of these data sets also allows detailed anatomical models to be built of the vascular and cranial structures, aiding in preoperative planning.¹⁸ Our focus in early and later imaging series is to understand principally the venous anatomy, as this is often the most challenging issue and early imaging can help determine if separation is even plausible. Computed tomography (CT) and magnetic resonance (MR) imaging will provide a preliminary understanding of the extent of fusion and the complexity of the shared arterial and venous architecture. With this imaging, we can proceed with more complex computer three-dimensional modeling as we transition from evaluation to the surgical planning phase.

Table 21.1 Surgical risk stratification	
Characteristic	Score
Scalp	
Minor surface area shared (< 10 cm ²)	1
Major surface area shared (> 10 cm ²)	2
Calvaria	
Minor surface area shared (< 10 cm ²)	1
Major surface area shared (> 10 cm ²)	2
Dura mater	
Independent dural envelope surrounding cortex	1
Dura shared along one or more planes	2
Neural tissue	
Completely separate	1
Interdigitated but not fused	2
Minor areas of fusion (total surface area < 5 cm ²)	3
Major areas of fusion or involvement of eloquent cortex (total surface area > 5 cm ²)	4
Arterial connections	
None	1
Minor feeding branches (M4, A4, P4)	2
Distal branches (M3, A3, P3)	3
Proximal branches (M2, A2, P2)	4
Major vascular trunks (M1, A1, P1, ICA)	5
Venous connections	
None	1
Separation of major sinuses with minor shared draining veins	2
Shared along anterior one-third of superior sagittal sinus	3
Shared distally (transverse/sigmoid)	
Shared along posterior two-thirds of superior sagittal sinus without involvement of the torcular	4
Shared along posterior two-thirds of superior sagittal sinus with involvement of the torcular	5
Deep venous drainage	
Present	1
Absent	2
Cerebrospinal fluid (ventricular anatomy)	
Separate ventricular systems	1
Shared ventricular system	2
Venous outflow	
Ipsilateral	1
Contralateral (crossed)	2
Arterial flow	
Ipsilateral	1
Contralateral (crossed)	2

Abbreviations: A, anterior (cerebral artery); ICA, internal carotid artery; M, middle (cerebral artery); P, posterior (cerebral artery).

Note: A higher score equates with more difficult separation. Minimum score, 10; maximum score, 28.

Source: Reproduced from Browd SR, Goodrich JT, Walker ML. Craniopagus twins. J Neurosurg Pediatrics 1:1–20, 2008.¹⁶



Fig. 21.5 Three-dimensional model based on computed tomographic and magnetic resonance imaging data of craniopagus twins separated at Montefiore. (Reproduced from Medical Modeling, Golden, CO, and from Douglas Cochrane, MD.)

Within the last several years, technology has afforded the ability to create detailed three-dimensional anatomical models sourced from DICOM (Digital Imaging and Communications in Medicine) data (► Fig. 21.5). Helical CT scanners can obtain high-resolution angiography that is comparable to traditional digital subtraction angiography, with these images converted to three-dimensional computer models for evaluation. The anatomical models can be customized to isolate particular anatomical features one might wish to study, such as the venous anatomy. High-resolution digital reconstructions of CT imaging combined with the three-dimensional models can help with assessment of the degree and orientation of bony fusion. This information is used in planning the surgical corridor, site of separation, and post-separation reconstruction of the cranial vault.

Highly detailed anatomical images from MR imaging provide evidence of shared cortex, ventricular anatomy, hydrocephalus/transepandyml flow, dural folds, or septa. Determining where normal and abnormal boundaries exist and having a full appreciation of each structure or vessel that is conjoined define the risk of surgery and impact the strategy employed during separation and reconstruction. The extent of shared vasculature is among the key factors in predicting successful separation. Advanced MR angiography and MR venography are able to provide crucial details regarding the vascular architecture—specifically, evidence of shared arterial communications and venous sinus, anomalous venous structures, and collateral or deep venous drainage. More experimental MR angiographic and MR venographic techniques now allow the characterization of arterial flow (vector and velocity). One can also evaluate for shared flow and determine which twin is getting the most arterial blood flow and then follow the shared changes during the staged separations.

Digital subtraction angiography remains the gold standard for assessing the complex vascular architecture seen in craniopagus patients. Angiographic studies aid in developing

the operative plan and determining which vessels should be sacrificed during surgery. Knowledge of the venous anatomy is particularly crucial at each step in a staged separation because as cortical veins are selectively pruned from the shared sinus and collateralization of the deep venous drainage occurs, new patterns of venous drainage may emerge. Preoperative planning should include a detailed analysis of arterial collateralization or cross-flow and the direction and degree of any cross-flow, identification of any shared venous anatomy or anomalous venous anatomy, and the direction and timing of venous outflow. All phases of a four-vessel cerebral angiogram, including the arterial and venous phases, should be carefully reviewed. One area of specific focus during the initial angiography session is the location of the cortical veins and their insertion points along the sagittal or shared sinus. It is critical to note any evidence of collateral/alternate venous drainage and the deep venous drainage patterns, and to determine any outflow dominance in the transverse sinuses. The external carotid circulation should be studied in detail for evidence of collateralization or retained fetal anastomosis.

Stereotactic imaging with both CT and MR has been a valuable adjunct and can be used for both preoperative planning and intraoperative guidance. Optical guidance systems are cumbersome because of the need for rigid fixation and light-of-sight issues; these can be especially problematic when the patient(s) need to be repositioned during a procedure, although newer magnetic tracking systems allow patient repositioning without loss of registration data. Functional MR imaging and positron emission tomography have been used in some cases to assess eloquent cortical areas. The practicality of functional imaging has to be assessed on an individual basis; however, any additional imaging studies that might provide useful for clinical or research data should always be considered.

21.5 Single-Stage Separation

Early neurosurgical pioneers and some contemporary colleagues advocate a single-stage operation in which the craniopagus patients are separated completely before they leave the operating room. The literature suggests that there has been limited success with single-stage separations as reported by other groups.²³ Conceptually and in practice, the surgery is undertaken as a surgical tour de force in which the case often lasts from 20 to 95 hours and involves several surgeons, who sometimes work in shifts during the procedure. Single-stage separation attempts are predicated on the presumed ability of the twins' venous drainage to function independently immediately at the time of separation. As the literature suggests, cases in which reconstruction of the sagittal sinus has been attempted²⁴ rarely meet with success because of the complexity of this procedure and the instant change in hemodynamic forces/stresses that occur when a bypass of the entire cerebral venous outflow is attempted. Our view is that the complexity of these cases almost always revolves around supporting or creating adequate venous outflow. Most commonly, one twin has reasonable outflow but the other does not. It is technically difficult, even with modern imaging techniques, to predict whether the preserved venous outflow channel can accommodate the sudden increase in

venous output at the moment of disconnection. If the surgical team is inaccurate in this assessment, a bypass must be performed (if it is not already planned for); otherwise, the patient will likely succumb to severe venous hypertension and the resultant complications, which can include stroke or death. For these and other reasons, we have favored a multiple-stage surgical approach.

21.6 Theory of Staged Separation

It is our collective opinion and experience that staging the separation affords a greater degree of safety and control than a single separation attempt. As we have discussed, the shared venous anatomy is the causal factor leading to the major surgical morbidity encountered in modern separation attempts.²⁵ Until recently, it was generally accepted that death or insurmountable neurologic deficits were to be expected in one twin secondary to the venous hypertensive bleeding that can occur during the final separation of the shared dural venous sinuses. In almost every case, the surviving twin received the entire superior sagittal sinus during separation. The twin that was lost had no suitable sinus, and either the bypass failed or the recipient's venous outflow channels were inadequate to handle the huge increase in venous outflow.

When the operations are staged, both twins can be prepared for the eventual separation with gradual occlusion of the venous outflow channels. This process of selectively pruning the venous outflow allows remodeling via collateralization of the venous outflow and the development of deep venous drainage. In contrast to acute venous occlusion, which is poorly tolerated because of venous hypertension, brain edema, and/or hemorrhage, gradual occlusion of the major venous structures is well tolerated by patients. A good analogy is a patient with a large parasagittal meningioma. These slow-growing lesions can occlude the posterior portion of the sagittal sinus, but patients rarely have venous hypertension as part of their presentation because collateral deep venous drainage has developed over time as the tumor grows. The staged approach allows the twin who will eventually be left without a functional sagittal sinus to develop a robust collateral venous drainage system that accesses the deep veins leading to the petrosal sinus or other deep venous outflow channels.

As we have previously reported,¹⁴ the process of collateralization is slow, and a staged separation generally requires many months from the initial procedure until the final separation, although the timing and length of the process will vary. To reach the final point of separation, it is now typical for craniopagus patients to undergo three to four staged procedures involving circumferential craniotomies and arterial-venous ligations. Patients are given a respite of 1 to 2 months between surgeries.²⁶

21.7 Surgical Techniques

The successful separation of twins depends on the ability to disconnect one twin from the shared sagittal or circumferential venous sinus. Most commonly, the vascular imaging studies demonstrate that one of the twins has most of the outflow to

the common sinus. The other twin generally displays evidence of a more robust deep venous collateral system. The twin with the more robust sagittal or circumferential sinus retains that structure, while the other twin (referred to as the "donor twin") undergoes forced collateralization and the development of deep venous drainage via pruning of the venous outflow to the shared sinus.

During the preliminary surgeries, several bridging veins are selected for pruning in the donor twin (► Fig. 21.6). Initially, temporary clips are placed across a bridging vein so that the venous drainage field can be monitored for evidence of venous hypertension. If brain swelling occurs or marked cortical erythema develops, indicating venous hypertension, alternate bridging veins can be selected for pruning, or the procedure can be aborted. A few bridging veins are ligated at each surgery to allow the gradual development of alternate deep venous collaterals. After partial disconnection procedures, we typically repeat MR imaging and angiographic imaging to look for changes in the venous outflow patterns in the donor twin. We repeat pruning surgeries until the donor twin is completely disconnected from the shared sinus and the final separation surgery can be undertaken.

21.8 Risks and Complications

The separation of craniopagus twins is fraught with potential complications that lead to various morbidities and potential mortality. The most dangerous risk at any given point among a myriad of possible complications is venous hypertension with subsequent intraparenchymal hemorrhage. The process of staged separation conceptually allows the development of more extensive deep venous drainage in the donor twin, mitigating this risk to some degree. At the time of surgical pruning, we strongly favor the use of intraoperative temporary clipping and inspection of the cortical areas for evidence of venous hypertension. This technique helps to prevent taking venous channels that are necessary for cortical drainage. Careful preoperative planning can assist with decisions as to which veins should be selected for pruning and how many veins should be selected at each operation. Reimaging the venous system after each surgery is critical to understand the result of a recent surgery and the changes that occur as deep venous collateralization develops over time as a direct result of the prior intervention.

Another issue associated with staged procedures is the need for the surgeon to maintain orientation, thus having a continuing knowledge of the overall anatomical location of the circumferential sinus and associated areas of conjoined brain tissue, and a concept of where the final ligation will occur.²⁶ The placement of Silastic sheets between adjacent cortical areas helps preserve the natural tissue planes and provides a means for reorientation at the time of repeated procedures.¹⁴

Fused cortical areas have commonly been reported in craniopagus twins. The strategy has been to coagulate and divide the shared cortex, and in most cases this has been well tolerated, without obvious deleterious cognitive consequences in the twins. As the degree of conjoined brain increases, so too does the risk for cortical damage (i.e., brain damage). In two cases in which we were consultants, the degree of fused brain was considered too significant and excessive for the twins to be

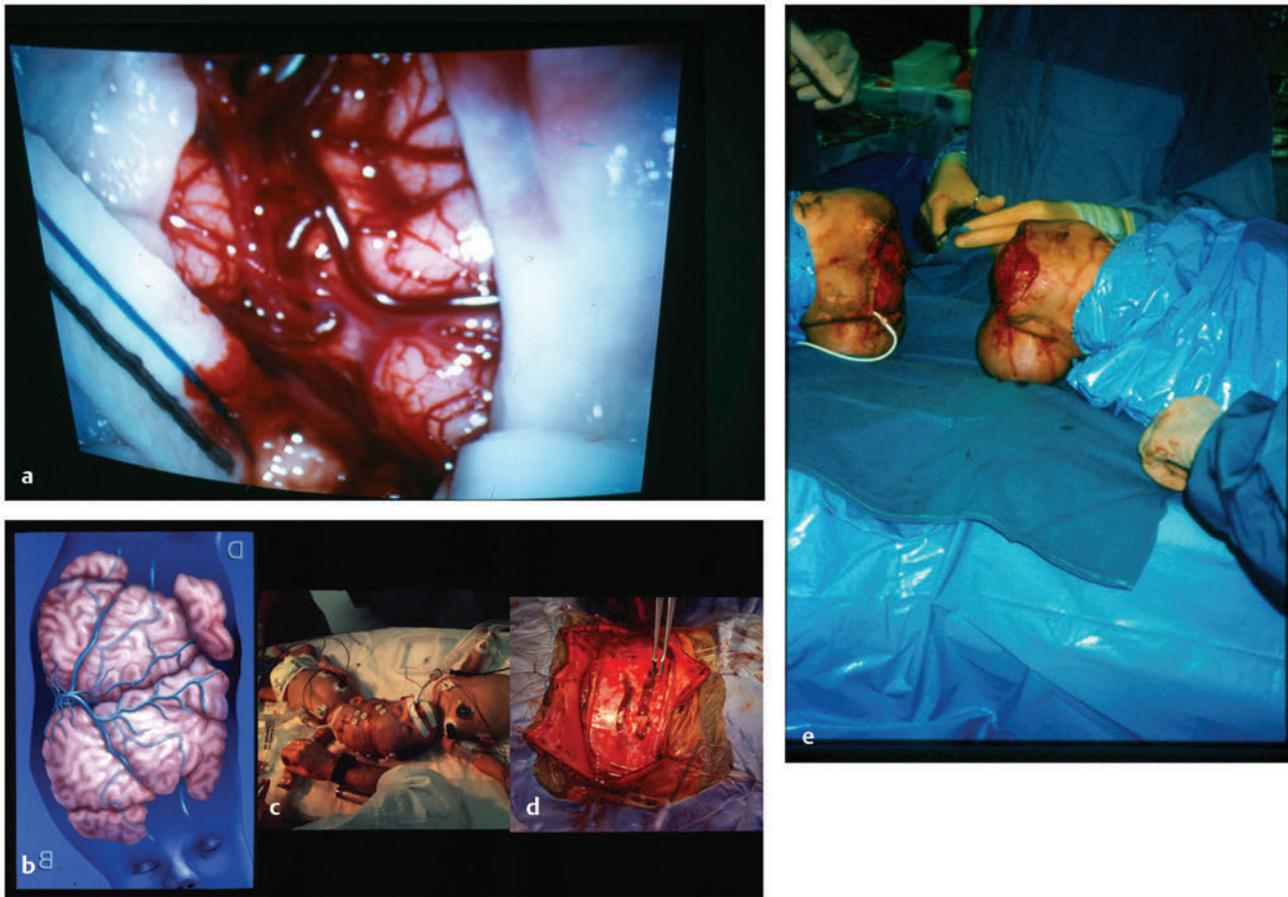


Fig. 21.6 (a) Intraoperative photograph showing pruning of a draining vein to the circumferential sinus. (b) Artist's representation of the first surgical stage: opening of a bifrontal flap and identification of the left between the two brain hemispheres. (c,d) Photographs showing intraoperative positioning and initial bifrontal flap and exploration. (e) Photograph showing the final separation of a set of twins in a staged approach. ([a] and [c–e] Reproduced from Browd SR, Goodrich JT, Walker ML. Craniopagus twins. *J Neurosurg Pediatr* 2008;1:1–20.¹⁶ [b] Republished from Walker M, Browd SR. Craniopagus twins: embryology, classification, surgical anatomy, and separation. *Childs Nerv Syst* 2004;20:554–566.¹⁴)

separated safely. Cross-filling of arterial blood between twins is also a possibility, and the surgeon must know the direction of flow and the contribution of the shared arterial branches to decide at what stage and in which location to coagulate the arteries to avoid significant ischemia. MR imaging vascular flow studies and conventional angiography can help in determining the timing and location.

Large scalp, skull, and dural defects created by the separation require reconstructive surgical repair for good functional and cosmetic outcome. As with many procedures, the dura is reconstructed with a variety of allograft products, including allograft dural substitutes. We have found, though, that the best dural defect repairs are those done with sewn-in grafts that can provide a watertight closure. If achieved, a watertight closure significantly reduces postoperative cerebrospinal fluid leaks, which can be devastating. The craniotomy flap is replaced and plated at each stage to provide stability. At the final separation, large calvarial defects can be left open for later repair, or the surgical team can fabricate split-thickness autograft to repair the defects. Some surgical teams have fabricated custom cranioplasties for later placement. Although these implants can lead to good cosmetic reconstructions of the cranial vault, the

long-term implications of a foreign body implant is not yet well documented. In our last two cases, we have repaired the calvarial defects with split-thickness grafts at the time of the final surgery, with good results to date.

Tissue expanders are used during the multiple surgical procedures to allow the growth of additional scalp, reducing the need for the incorporation of rotational or transpositional flaps.¹⁴ Tissue expanders have also been used on a longer-term basis (3 to 6 months) before a single-separation procedure.²⁷ We advise delaying the placement of the tissue expanders during staged separations until the penultimate procedure to avoid the common complication of cerebrospinal fluid leak and infection. We have also learned that the expansion can never be too large. Working with the plastic surgeons, we take advantage of every space of scalp expansion. During the final procedure, the expanded scalp will naturally contract, resulting in less tissue, so over-expansion is critical.

Despite the absence of major portions of the dura mater, falx, and superior sinuses, craniopagus twins do not present with hydrocephalus, which indicates that cerebrospinal fluid is being rerouted and adequately reabsorbed.²⁸ Gradual surgical separation, however, may alter the absorptive capacity in one or both

twins, leading to the need for cerebrospinal fluid diversion. Routine postoperative CT and MR imaging may provide evidence of hydrocephalus, and shunt placement can be carried out as the need arises. With the use of the staged procedure, the incidence of hydrocephalus requiring cerebrospinal fluid diversion has been dramatically reduced.

The potential for infection during multiple-stage surgical procedures is high, and postoperative infections can occur. Indwelling catheters, shunts, tissue expanders, and drains used during this prolonged period provide a direct route for infection. We no longer routinely use subgaleal drains, to avoid both infections and possible cerebrospinal fluid fistulas. To reduce the risk for infection, we use antibiotics routinely during and after surgery and minimize the use of potential vehicles for infection.

21.9 The Socioeconomic Ethics of Craniopagus

Beyond the ethical dilemma inherent in a surgery that has such high risk for one or both of the individuals involved, in a world with limited medical resources, the justification to separate craniopagus twins often meets with cynicism on many fronts. The cost of taking a separation attempt from work-up to discharge can run upward of 2 million dollars or more if the procedure occurs in the United States. It is also likely that the children will need further care and extended follow-up after surgery, raising the cost of care even more. Furthermore, many craniopagus twins come from developing nations, and the inability of the home country or indifference of the host nation to support such a medical feat leaves the burden to charitable individuals or organizations. The arguments presented and ethical dilemmas often raised relate to the fair allocation of resources. To put this into perspective, 2 million U.S. dollars in sub-Saharan Africa can provide over 570,000 pneumococcal vaccinations, with unquestionable benefit to the larger society as a whole. In a world with limited resources, it is not unfair to question the allocation of resources to two individuals. Nonetheless, a clear desire to help and our quest to take on the most challenging of cases and advance the practice of neurosurgery often supersedes these concerns. Yet, the cultural and religious significance associated with craniopagus twins cannot be underestimated. We have had several experiences in which families wanted no intervention because they viewed the birth as a “warning from God” or an omen. In such situations, decision making moves from the medical realm back to the medicoethical realm and becomes even more fraught with complications.

21.10 Nonoperable Craniopagus

Although surgical technology and the practice of neurosurgery are ever advancing, inoperable cases of craniopagus do occur. The factors that generally preclude operability are shared venous anatomy and less frequently shared eloquent structures. Patients with complex venous anatomy and fusion anomalies that equate to craniopagus risk stratification scores in the upper 20s are still thought to have inoperable craniopagus. As an example of shared eloquent brain, we reviewed a case of angular craniopagus twins joined side to side along the parieto-occipital regions. Imaging studies demonstrated a shared central diencephalon

with an anatomical diencephalic bridge. Because of the severity of the conjoining along the midline, it was believed the risks of surgery were unacceptably high, and separation was not performed. Another case was found to be inoperable because of an extensive shared central venous anatomy. This set of nonoperable craniopagus twins had a partial angular frontal configuration; the twins were conjoined at the forehead with a shared anterior fontanel, and both were neurologically intact. At day 25, twin B developed respiratory distress, leading to cardiac arrest. The premature death of twin B necessitated an emergency separation attempt, which was unsuccessful. With ever-improving surgical technology and continued advances in our understanding of the complex physiology in craniopagus twins, it is our hope that eventually techniques will be developed to separate those whose condition is now considered inoperable. Nevertheless, sometimes the anatomical conjoining is just too complex, with surgical attempts leading to unacceptable risks and predicted bad outcomes, such that separation will not be achievable.

21.11 Summary

The separation of craniopagus twins represents one of the most challenging neurosurgical endeavors. Advances in our ability to obtain high-resolution imaging have furthered our understanding of the complex anatomy present in these individuals and form the foundation for any attempted separation. The social, ethical, and financial considerations of attempting a separation cannot be understated. Although surgical technology and our understanding of craniopagus physiology have advanced tremendously in the more than 60 years since the first successful separation, these cases remain humbling, and patients present whose cases are still inoperable, even with modern neurosurgical techniques and understanding.

Pearls

- As technology and our understanding of the complex craniopagus anatomy has grown, it is now recognized that the presence of shared dural venous sinuses is among the most challenging issues faced in any separation attempt.
- A high-quality preoperative evaluation with clinical monitoring, imaging, and anatomical modeling can determine which patients are truly inoperable.
- When the operations are staged, both twins can be prepared for the eventual separation with gradually occlusion of the venous outflow channels. This process of selectively pruning the venous outflow allows remodeling via the collateralization of venous outflow and the development of deep venous drainage.

At the time of surgical pruning, we strongly favor the use of intraoperative temporary clipping and inspection of the cortical areas for evidence of venous hypertension to prevent taking venous channels that are necessary for cortical drainage.

- The placement of Silastic sheets between adjacent cortical areas helps preserve the natural tissue planes and provides a means for reorientation at the time of repeated procedures.
- Tissue expanders used during the multiple surgical procedures allow the growth of additional scalp, reducing the need for incorporation of rotational or transpositional flaps.

21.12 Acknowledgments

For further information on the history and management of craniopagus twins, refer to the articles by the authors on which this chapter was based.

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22 Open Fetal Surgery for Myelomeningocele

Nalin Gupta

Fetal surgery arose in an effort to improve the outcome of patients with specific developmental anomalies, such as congenital diaphragmatic hernia and bladder outlet obstruction, that were often fatal, either in utero or immediately after delivery.¹ Because the pathologic effects of these disorders appeared to worsen during gestation, pediatric surgeons began to realize that early intervention, preceding irreversible physiologic sequelae, could improve survival, and perhaps functional outcomes. The technical steps that were required to achieve the goal of successful fetal surgery with acceptable maternal morbidity took decades to develop, initially in a nonhuman primate model.^{2,3}

The primary difference between fetuses with open neural tube defects (NTDs) and those with other diseases is that the anomaly is not fatal if untreated, gestation is usually carried to full term, and NTDs are not usually associated with other major organ defects.⁴ This is an ethical challenge for treating physicians because the potential benefits of prenatal intervention must be balanced by well-defined risks to the fetus and the mother, who is a “bystander” with respect to the perceived benefits—that is, she undergoes significant surgical risk but accrues no direct medical benefit. The ethical considerations of fetal surgery are most analogous to living related organ transplantation.

Fetal surgery requires the active participation and interaction of several clinical teams. Each group has a specific role, with overlap often required at different points of the evaluation and treatment plan. A multidisciplinary approach is mandatory in order to accomplish the surgical goals with acceptable clinical outcomes. Regular case discussions allow a joint review of prospective patients and their preoperative considerations, as well as ongoing follow-up of postoperative patients. Extensive counseling with the patient and family is critical before the patient can be expected to reach a carefully considered decision and before informed consent can be obtained. The risks and benefits of fetal surgery, as demonstrated by the recently published results of the Management of Myelomeningocele Study (MOMS), are described later in this chapter.⁵

22.1 Rationale for Fetal Repair

Although myelomeningocele is a defect of central nervous system (CNS) development, the impact upon other organ systems contributes to a substantial burden of disease.⁶ Despite aggressive postnatal intervention, nearly 14% of children with NTDs do not survive past 5 years of age, and the mortality rises to 35% among those with symptoms of brainstem dysfunction secondary to the Chiari 2 malformation.⁷ Although 70% of affected individuals have an IQ above 80, only 37% are able to live independently as adults.⁸

Although there is a broad spectrum of severity, it is useful to separate the neurologic deficits into two groups: primary and secondary. The primary neurologic deficits are those directly caused by the arrested development of the neural placode, which usually occurs in the lumbosacral region.^{9,10} Because

neural tube closure occurs during the third and fourth weeks of gestation, the spinal cord in this region is very immature at the stage when a myelomeningocele develops. Although the structure of the spinal cord is severely disrupted at the involved level, it is unknown whether the placode is capable of further development.¹¹ The functional neurologic level is either at the same level as the vertebral anomaly or actually higher, resulting in worse neurologic function in more than 80% of patients with open NTDs.¹²

The secondary neurologic deficits in patients with spina bifida include delayed loss of motor function, worsening bowel and bladder control, and scoliosis. Magnetic resonance (MR) imaging studies of most myelomeningocele lesions following repair show a dysplastic spinal cord terminating in the overlying soft tissues at the site of the repaired defect. Because the normal dura and other dorsal tissues are absent, the surgically separated placode is almost always attached to the overlying by scar tissue. At least by radiologic and anatomical features, virtually all patients with a true myelomeningocele have a tethered spinal cord. It is unclear what factors lead to the development of new symptoms attributable to the tethered spinal cord in some patients and not in others. Another source of confusion is that the symptoms and signs typically attributed to a tethered spinal cord can be caused by other conditions, such as a Chiari 2 malformation, a spinal cord syrinx, or hydrocephalus.

22.2 Preclinical Research

Fetal surgery for a variety of conditions was systematically developed in a series of consistent steps, beginning with proof of concept in an animal model, definition of the natural history in utero, refinement of surgical techniques in test cases, and finally evaluation of efficacy in a prospective randomized clinical trial.

The theoretical advantage of fetal repair for myelomeningocele is that the neural tube is covered and protected for many months before the expected delivery date. The basis for anticipating improved neurologic function is that restoration of the dysplastic neural placode within the spinal canal isolates it from the amniotic fluid and prevents ongoing injury.^{13,14} An ideal animal model that would occur as a spontaneous lesion and allow surgical access with measurement of outcome does not exist. In order to test fetal intervention, Meuli et al surgically created a spinal cord lesion in fetal sheep at 75 days of gestation that simulated a spina bifida lesion.^{3,15,16} A laminectomy was performed to expose the fetal spinal cord at 75 days of gestation, and the pregnancy was allowed to continue. The lambs were delivered by cesarean section at 140 days of gestation. After delivery at term, the gross and microscopic appearance of the exposed spinal cord resembled a human spina bifida lesion, and the animals were incontinent and had loss of sensation and motor function below the lesion level. One group of animals with surgically created spina bifida lesions were then treated with a myocutaneous flap at 100 days of gestation. These animals were then carried to full term and had nearly normal

motor function and normal bowel and bladder control. The results of these experiments suggest that early repair of an exposed spinal cord may preserve neurologic function and may allow improvement through plasticity. Additionally, in a separate set of animal experiments, hindbrain herniation mimicking the Chiari malformation was created by creating a cerebrospinal fluid (CSF) leak in the spinal canal; hindbrain herniation was reversed by fetal repair in the lambs.¹⁷ Although provocative, these large animal experiments clearly rely on a model system that has distinct differences from the human disease.

22.3 Initial Fetal Surgery for Myelomeningocele

The first cases of fetal myelomeningocele repair were performed in 1994 with an endoscopic technique,¹⁸ followed by an open hysterotomy approach.^{19,20} These early experiences were encouraging in that some of the secondary neurologic features associated with myelomeningocele, such as hindbrain herniation and hydrocephalus, were potentially reversible.^{21–24} In the combined series of patients undergoing fetal surgery from The Children's Hospital of Philadelphia, and Vanderbilt University (Nashville, TN), 104 patients followed for at least 1 year had an overall incidence of shunting of 54%, compared with 86% in a historical control group from The Children's Hospital of Philadelphia.²⁵ The effect was most evident for those with lumbar lesions. The incidence of shunting in those patients who underwent fetal closure before 26 weeks of gestation was 42.7% but was 75% in those who had fetal surgery after 25 weeks of gestation. Although speculative, a potential mechanism explaining this improvement is that chronic CSF leakage and a reduction in subarachnoid pressure during fetal development lead to both hindbrain herniation and eventual permanent failure of CSF absorption. Interpretation of the results of these early case series was limited by selection bias and the lack of true control arm.

22.4 Management of Myelomeningocele Study

22.4.1 Study Design

Prospective randomized surgical clinical trials are difficult to conduct for a variety of reasons. The complexity, controversy, cost, and risks of fetal surgery, however, provided a stronger rationalization for examining these novel techniques in rigorous clinical trials. Other conditions treated by fetal surgery, such as congenital diaphragmatic hernia and twin–twin transfusion, have been successfully studied with a randomized clinical trial design. Therefore, once the feasibility of fetal repair for myelomeningocele and a possibility of benefit had been demonstrated in pilot studies,^{22,26–28} the logical next step was to conduct a randomized trial to determine if a real benefit was present.

The design of MOMS required an initial screening by a non-surgical coordinating center (George Washington University, Washington, DC), and if patients met the inclusion criteria, they traveled to one of three surgical institutions—The Children's Hospital of Philadelphia, Vanderbilt University, or the

University of California at San Francisco. Additional evaluation was performed at the surgical sites, and if consent was provided, the patient was randomized into either a postnatal or a prenatal treatment arm. Mothers sometimes stayed for many weeks at the study site, depending upon the development of any complications.

An unusual feature of the trial was the development of two primary clinical outcomes. First was the need for a ventricular decompressive procedure, usually a ventriculoperitoneal (VP) shunt, for the treatment of hydrocephalus. The second primary outcome consisted of a composite score derived from the Bayley Scales of Infant Development and the difference between motor function and lesion level. A great deal of planning was done to minimize the impact of bias. Because there are recognized variations in practice across the country, simply receiving a VP shunt was not a satisfactory outcome measure for evaluating hydrocephalus. Therefore, objective shunt criteria were created, and an outside panel of pediatric neurosurgeons, blinded to type of repair, were assigned to determine whether the subjects met those shunt criteria. For neurologic outcomes, the subjects were examined in a blinded fashion by an independent group of specialists not associated with any of the surgical sites.

22.4.2 Results

MOMS was halted after 183 subjects, of the planned 200, had been recruited. An interim analysis of 158 subjects who had reached 12 months of age and of 138 who had reached 30 months of age demonstrated efficacy. The two treatment groups did not differ in terms of maternal age, body mass index, or gestational age at the time of surgery. The lesion level was higher in the fetal treatment group, with 33% having a lesion at L2 or higher, compared with 17% in the postnatal group. In terms of the treatment of hydrocephalus, by objective criteria, 65% of the subjects in the fetal group met previously determined shunt criteria, compared with 92% of the postnatal group (a significant difference; $p < 0.001$). Of note, the treating neurosurgeons at the family's community were not blinded to the treatment that patient had received, and in the fetal group, only 40% actually received a shunt, compared with 82% in the postnatal group.

The difference in the second primary outcome, determined at 30 months after birth, also reached statistical significance ($p < 0.007$), with the difference between motor function and lesion level higher than expected in the fetal treatment group. The difference in the other component of this outcome measure, the Bayley Scales, was not statistically significant. The most striking difference was the presence of hindbrain herniation, with 76% of the fetal group having none or a mildly severe form and 67% of the postnatal group having a moderate or severe form (► Fig. 22.1). Finally, twice as many of the fetal group (42%) were ambulating at 30 months than of the postnatal group (21%).

The maternal risks in the fetal group were notable: chorioamniotic separation (26%), oligohydramnios (21%), need for blood transfusion at delivery (9%), placental abruption (6%), and pulmonary edema (6%). Although there were 2 fetal or neonatal deaths in each group, fully 80% of the fetal group were delivered prematurely (before 36 weeks of gestational age), compared with 15% in the postnatal group.



Fig. 22.1 Effect of fetal closure on hindbrain appearance. (a) Fetal sagittal magnetic resonance (MR) image showing a tight posterior fossa with tonsillar descent into the upper cervical spine. (b) MR imaging (T1-weighted sagittal sequence) after delivery showing near-normal appearance of the cerebellum with normal-appearing brainstem morphology and the presence of a cisterna magna. (Reproduced with permission of the publisher from Jallo G, Kothbauer KF, Pradilla G, eds. *Controversies in Pediatric Neurosurgery*. New York, NY: Thieme Medical Publishers; 2010: chap 16.)

22.4.3 Interpretation of Results

MOMS required nearly 10 years to complete with the active participation of several large clinical and research teams. Despite its complexity, the results obtained are relatively clear. The fetal treatment group, despite having a higher lesion level, had better clinical outcomes in terms of hydrocephalus, Chiari malformation, and ambulation. Several caveats must be recognized. First, the outcomes were measured at 12 and 30 months. It is possible that these benefits are not durable and will not persist throughout life. Second, although the differences in the anatomical appearance of the hindbrain herniation and in the reduction of treated hydrocephalus appear real, whether these will result in a meaningful difference in outcome and reduction in morbidity is unknown. A long-term follow-up study of the two treatment groups from MOMS is under way, and it is hoped that it will provide some of the answers to these questions. The final important point is that the risks of the procedure are defined. These include prematurity, maternal complications, and the impact on future pregnancies. They are not to be underemphasized when fetal surgery is being considered.

22.5 Planning and Conduct of Fetal Surgery for Myelomeningocele

22.5.1 Initial Evaluation

From a theoretical perspective, fetal repair should be performed as early as possible. In practice, surgical timing is determined by the existing standards of prenatal care in normal pregnancies. Most myelomeningoceles are detected during the second trimester, either during an investigation of a positive maternal serum screening test (i.e., elevated maternal serum level of alpha fetoprotein) or during a routinely scheduled fetal anatomical ultrasound survey (usually scheduled at or after 18 weeks of gestation). The quality of current ultrasonography allows the detection of most fetuses with myelomeningoceles by the middle of the second trimester.²⁹ From a practical viewpoint, this means that a diagnosis is most often made between 18 and 22 weeks of gestation. It is unlikely that the detection of fetuses affected with spina bifida will occur any earlier unless more sensitive screening tests become widely used.

22.5.2 Preoperative Screening

Patients referred to a fetal surgery center should undergo a preliminary screening evaluation to confirm if an in-person evaluation is appropriate. An evaluation of the mother's risk as a surgical candidate requires recorded information of all physical examinations and the medical, surgical, and anesthetic history. A normal fetal karyotype is required if a patient is to be considered a potential candidate for prenatal fetal surgery. Before any decision is made by the patient and surgical team that leads to fetal surgery, a detailed evaluation at the fetal surgery center is required. This includes but is not restricted to:

- Comprehensive obstetric ultrasonographic examination, including documentation of the cervical length, placental location, fetal gestational age, degree of fetal kyphosis, level of the myelomeningocele, lateral ventricular size, presence (and severity) of a Chiari malformation, leg and foot position, lower extremity movement, and presence or absence of placenta previa or other potential contraindications to fetal or maternal surgery
- Fetal echocardiography, to exclude any concurrent/occult structural cardiac defects
- Fetal MR imaging of the brain and spine to confirm and supplement the sonographic findings
- Maternal physical examination and consultation by anesthesia and perinatology
- Psychosocial evaluation to identify maternal suitability for surgery. In addition to being screened for depression and anxiety, it is critical that the patient have adequate support available to accommodate her inability to care for herself and her other children for most of her pregnancy following prenatal surgery, and that she be capable of understanding and complying with the lifelong proscription against labor.
- Preoperative teaching about NTDs, latex allergy, and community resources; perioperative instruction regarding the surgery itself and the tocolytic program; postoperative management in the hospital; postoperative care and recommendations following discharge; prenatal care; recommendations for the continued care of the child

22.5.3 Imaging Studies

A detailed sonographic examination is able to determine a number of anatomical features with precision. These include the size of the overlying CSF-containing sac, the level of the

defect, the position of the cerebellar tonsils, the presence of lower extremity deformities, and potential concurrent non-neurologic anomalies. The limitations include difficulty in determining the number of associated brain anomalies, other intraspinal anomalies, and at times the exact dysraphic level.

Mothers should also have a fetal MR imaging study of the brain and spine. In order to minimize the effects of fetal motion, images in sagittal, axial, and coronal planes are obtained randomly by repeatedly imaging the fetus over time. The preferred MR imaging technique is a single-shot, fast spin-echo T2-weighted sequence. Evidence suggests that MR imaging may improve the ability to detect coexisting spinal and brain anomalies that may not be apparent on ultrasound studies.^{30,31}

22.5.4 Maternal Counseling and Informed Consent

In order for the patient and family to provide a truly informed consent, every effort must be made to present an unbiased and balanced description of the potential benefits of prenatal myelomeningocele repair versus the surgical risks. Potential candidates for fetal surgery should meet with all members of the team: fetal surgeon, perinatologist, pediatric neurosurgeon, anesthesiologist, social worker, and spina bifida nurse coordinator. Critical issues for discussion include the following: (1) maternal surgical risk; (2) risk for preterm birth that would otherwise be essentially nonexistent, and the sequelae of preterm birth at a variety of gestational ages; (3) details of the postoperative course, which can be quite challenging and unexpected for a previously healthy patient; (4) potential postoperative complications, such as tocolytic toxicity, pulmonary edema, blood clots, oligohydramnios, and preterm premature rupture of membranes (PPROM); (5) risk for uterine dehiscence and rupture in the setting of a fresh hysterotomy, (6) need for the avoidance of labor and the requirement for cesarean delivery in all future pregnancies; and (7) a balanced and accurate review of the outcomes reported in MOMS.

Maternal risks of the procedure are those of general and regional anesthesia, bleeding and the potential need for blood products, and intraoperative complications, including the need for fetal resuscitation and, rarely, fetal death or maternal death. Additional maternal risks include postoperative complications, such as infection, pulmonary embolism, and oligohydramnios; however, the most common complication is that of preterm labor and preterm birth. It is essential for parents to understand that a pregnancy complicated by a fetal myelomeningocele that does not undergo fetal surgical repair has the same risk for preterm birth as that of the general obstetric population—and that this risk is significantly increased by prenatal surgery with an open hysterotomy. Neurologic outcomes for infants with a myelomeningocele may be compounded by complications of prematurity that might not have otherwise happened, particularly if delivery occurs at a vulnerable gestational age. These risks are weighed against the potential benefits and the improved quality of life that those affected by spinal cord defects may experience following prenatal surgical repair.

22.5.5 Anesthetic Considerations

Open fetal procedures that require a uterine incision (e.g., myelomeningocele repair) are performed under general anesthesia,

which provides the needed uterine relaxation with the use of volatile anesthetic agents. In fact, the primary difference between fetal surgery and a cesarean delivery is that with the latter, the normal reflexive uterine contraction is relied upon to help achieve hemostasis. During fetal surgery, the same contractile force would result in inadequate blood flow to the umbilical cord and potential placental separation, which must be avoided.

The potential consequences of the profound uterine relaxation achieved with this approach to anesthesia include an increased potential for significant maternal hypotension resulting in decreased uterine blood flow and alterations in fetal hemodynamics. An epidural catheter is typically placed preoperatively for smoother emergence from general anesthesia and for postoperative analgesia. The advent of instrumentation specifically designed for fetal surgery has been critical in helping to prevent hemorrhage that would otherwise result in the setting of the necessary uterine relaxation and a fresh uterine incision.

22.5.6 Preoperative Treatment

Preoperatively, a nonparticulate antacid is given for prophylaxis against aspiration, rectal indomethacin is placed as an additional prophylactic tocolytic, and an epidural catheter is inserted. The position and efficacy of the epidural catheter are verified with a preoperative test dose (epidural placement often occurs before entry into the operating room, allowing time for a test dose). Blood products (type and crossmatch) are obtained for both mother and fetus. Sequential compression devices are placed on the mother's lower extremities to minimize the risk for deep venous thrombosis. Minimal doses of preanesthetic medications (opioids or anxiolytics) are administered in order to reduce the incidence of hypotension when maximal doses of a volatile halogenated agent are administered. When any general anesthetic is administered after approximately 20 weeks of gestation, the patient is (1) positioned with left uterine displacement and (2) adequately preoxygenated, after which (3) rapid-sequence induction and tracheal intubation are performed with cricoid pressure. Before incision, anesthesia is typically maintained with low concentrations of a volatile agent. During this time, the sonologist determines the fetal presentation and maps out the placental location and edges, additional large-bore vascular access is obtained, the urinary bladder is catheterized, and prophylactic antibiotics are administered.

22.5.7 Intraoperative Treatment

During surgery, 2 to 3 MAC (minimal anesthetic concentration) of a volatile anesthetic agent are used to provide maternal and fetal anesthesia and surgical tocolysis (uterine atony). Volatile anesthetic agents inhibit myometrial contractility by calcium-sensitive potassium channel modulation.³² The human uterus has a thick, muscular layer that is sensitive to stimulation or manipulation. Thus, uterine incision and stimulation may produce strong uterine contractions. Halogenated anesthetics cause a dose-dependent inhibition of uterine contractions and myometrial tone. Complete uterine relaxation is essential because increased uterine tone compromises uterine perfusion, especially during uterine manipulation. The increased tone increases the risk for partial placental separation. When needed,

high doses of intravenous nitroglycerin may also be used as a supplemental agent for intraoperative uterine relaxation.³³

Once hysterotomy closure begins, the inspired concentrations of halogenated agents are slowly decreased. Discontinuing a high-dose volatile halogenated agent at the beginning of surgical closure allows more time for its elimination from the tissues. To combat the increase in uterine tone that results when volatile gas concentrations are decreased, a loading dose of 4 to 6 g of magnesium sulfate is simultaneously administered intravenously over 20 minutes, followed by a continuous infusion of 1 to 2 g/h. This infusion continues for at least 24 hours postoperatively in an attempt to maintain uterine relaxation and minimize postoperative contractions (see later section on postoperative care). Intraoperatively, maternal intravenous fluids are restricted (<2 L) in order to minimize the risk for postoperative pulmonary edema, which is often associated with the use of tocolytic agents,^{34,35} particularly in the context of maternal surgery and general anesthesia. Inspired halogenated agents are discontinued once the continuous infusion of magnesium sulfate is running, and maternal anesthesia is maintained by the activation of epidural anesthesia and the intravenous administration of fentanyl and/or nitrous oxide in oxygen. If neuromuscular agents are utilized, the absence of neuromuscular blockade should be determined before tracheal extubation because magnesium sulfate potentiates neuromuscular blockade.

Whatever anesthetic technique is used for open fetal surgery, it must ensure adequate uteroplacental perfusion, profound uterine relaxation, maternal hemodynamic stability, fetal anesthesia and immobility, and minimal fetal myocardial depression and compromise. Excessive volume replacement should be avoided—particularly in conjunction with maternal tocolysis—in order to prevent maternal pulmonary edema, which has historically been a significant cause of postoperative morbidity.

22.5.8 Hysterotomy and Exposure

Successful open fetal surgery requires the execution of several critical technical steps: (1) optimizing the hysterotomy location, (2) opening the highly vascular and perfused gravid uterus with a minimum of bleeding while simultaneously preventing separation of the chorioamniotic membranes, (3) ensuring fetal stability throughout the procedure, (4) maintaining uterine relaxation, (5) achieving a watertight closure of the hysterotomy following the reinfusion of fluid into the amniotic cavity at the conclusion of the procedure, and (6) initiating aggressive intraoperative tocolysis before extubation to prevent preterm labor.¹

An epidural catheter is placed and a test dose given before the procedure, so that it is ready for use immediately postoperatively for pain control. The patient is then anesthetized with a halogenated agent for uterine relaxation. The fetus is monitored throughout with continuous intraoperative ultrasound and, when necessary, fetal echocardiography. A generously sized low transverse maternal skin incision is made and carried through the fascia and into the intraperitoneal cavity. For optimal exposure, and to prevent compression of the engorged uterine vessels, the medial portion of the maternal rectus muscles may be split and the epigastric arteries identified and ligated. The uterus is exposed and the placental location re-evaluated. If the placenta is completely anterior, the uterus will be delivered and tipped forward to allow posterior surgical access. The fetal lie is

evaluated by the perinatologist for optimal surgical positioning; if needed, an external version can be performed at this time through the relaxed, hypotonic uterus, so that the incision can be placed directly over where the fetal back is positioned. Before hysterotomy, a narcotic is administered to the fetus intramuscularly with ultrasound guidance (usually in the shoulder or rump). With care taken to avoid the placental edge, the hysterotomy is initiated with the placement of two stay sutures that will be utilized to place a specially designed absorbable uterine stapler device that provides hemostasis and seals the membranes to the myometrium.

The uterine incision is usually between 6 and 8 cm in length. After the hysterotomy is completed and hemostasis is ensured, a catheter is placed into the uterus to allow the continuous infusion of warm lactated Ringer solution around the fetus to maintain fetal temperature and avoid umbilical cord compression. With the continuous infusion of fluid, the fetus will float in the uterine cavity, which helps to push the torso upward against the open hysterotomy. This is preferred because the fetus will otherwise tend to move or drift during the surgery, which can make the neurosurgical repair difficult. The fetus is rarely removed from the uterus in order to avoid unnecessary manipulation, dehydration, hypothermia, or umbilical cord spasm. After repair of the fetal defect, a two-layer closure of the hysterotomy is begun, and several boluses of warm lactated Ringer solution are added through the catheter to restore a low-normal amniotic fluid level (as determined by intraoperative ultrasound).

22.5.9 Surgical Repair of the Fetal Defect

The anatomical features of the fetal myelomeningocele defect are visually very distinct, and determining the different structures is easier than at full term. The neural placode is always in the midline surrounded by an extremely thin layer of translucent arachnoid (► Fig. 22.2a). If the myelomeningocele sac is present, the placode is usually lifted upward away from the surface of the back. In some other situations, the placode is flat and at the same level as the surrounding skin. The epithelium of the skin does not usually reach the edge of the placode. The clear identification of the intervening arachnoid usually allows the placode to be divided from its attachments with sharp dissection.

The general steps of the actual fetal repair are very similar to those of the postnatal procedure. These include the following: (1) identification of the neural placode, (2) separation of the placode from the surrounding epithelium, (3) identification and closure of the dura, and (4) elevation of the surrounding soft tissues and closure of the skin. The major difference between the pre- and postnatal procedures is the tenuous nature of the fetal tissues. The neural placode is extremely fragile, and even limited manipulation leads to a loss of tissue integrity. Although the nerve roots are able to withstand some handling, excessive tension will cause avulsion from the placode. The dura is often insubstantial, is transparent when mobilized, and has the characteristics of arachnoid in older children. The fetal skin can withstand surgical dissection, but excessive tension leads to tearing.

The dura is loosely attached to the underlying subcutaneous tissues just lateral to the spinal canal. After the dura has been incised at its lateral junction with the dermis, gentle instillation



Fig. 22.2 Fetal closure of a myelomeningocele lesion. (a) The fetal myelomeningocele is framed in the hysteroscopy incision. The fetus is not removed from the uterus, and every effort is made to maintain the amniotic fluid volume. The actual sac consists of thin membranous tissue with a minimum of skin extending upward toward the placode. (b) The skin is closed as a single layer, in this case without a patch being required. (c) After delivery at 36 weeks, the wound appears well closed, although the sutures, which are of the monofilament absorbable type, are still visible. (Reproduced with permission of the publisher from Jallo G, Kothbauer KF, Pradilla G, eds. *Controversies in Pediatric Neurosurgery*. New York, NY: Thieme Medical Publishers; 2010, chap. 16.)

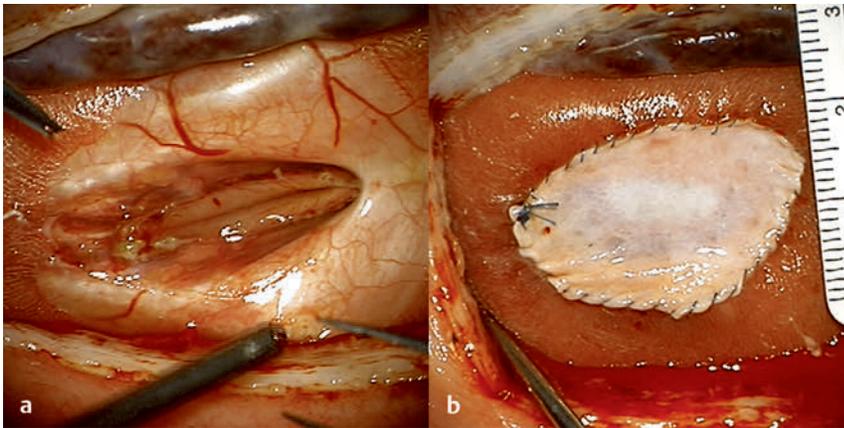


Fig. 22.3 (a) A flat myelomeningocele without a sac. The placode is visible in the center, and there is relatively little skin that can be mobilized to cover the defect. (b) The placode was successfully mobilized, but the skin closure was supplemented with a patch. (Reproduced from Gupta N, Rand L, Farrell J, Cauldwell C, Farmer D. Open fetal repair for myelomeningocele. *J Neurosurg Pediatr* 2012;9:265–273.)

of saline into the epidural plane with a small angiocatheter lifts the dura away from the underlying tissues, which minimizes trauma. Between 18 to 20 weeks of gestation, the dura can be very thin and difficult to handle. After 22 weeks of gestation, the dura becomes more substantial and can be handled more easily. Once the dura is circumferentially detached from the dermis and separated from the underlying lumbar fascia, it can be closed with a running suture. If the amount of dura is insufficient, then a patch is used to close the opening. The use of acellular human dermis to repair the dura may contribute to the formation of intracellular dermoid cysts.³⁶ For this reason, a synthetic collagen matrix (DuraGen; Integra NeuroSciences, Plainsboro, NJ) can be used to create a dural barrier.

Following dural closure, the fetal skin is closed as a single layer incorporating the superficial and deeper tissues (► Fig. 22.2b). In general, dissection of the underlying muscle and fascia is not attempted because excessive fetal blood loss must be avoided and the duration of the procedure minimized. Elevation of the skin and separation from the underlying subcutaneous tissues are relatively easy, although increased tension on the skin inevitably leads to tearing. Small openings in the skin caused by handling with forceps or tension from suture

points generally close rapidly. If the skin can be brought together, the final postnatal appearance is often excellent (► Fig. 22.2c). For situations in which insufficient skin is available to close the lesion, either skin flaps, relaxing incisions, or acellular dermis can be used as a patch (► Fig. 22.3). In most cases, this patch becomes incorporated into the healing scar tissue. In general, we have avoided relaxing incisions because they often create disfiguring scars later in life.

22.5.10 Postoperative Maternal Considerations

During the first several postoperative days, uterine quiescence is maintained with the use of multiple concurrent tocolytics, and the patient is observed for associated complications during a standard surgical recovery from a major abdominal laparotomy during pregnancy. Postoperative care includes a slow reintroduction of oral intake, intravenous hydration with care to maintain fluid balance, oxygen administration by either nasal cannula or mask, electronic fetal monitoring to assess fetal well-being and uterine contractions, insertion of a Foley catheter, tocolytic therapy, and use of an epidural catheter for

pain management. The patient is unable to ambulate for at least the first 2 days postoperatively, primarily because of the presence of the epidural catheter and the effects of muscle relaxation secondary to the continuous infusion of magnesium sulfate.

Postoperative complications include pulmonary edema, oligohydramnios, PPRM, and preterm labor. Pulmonary edema is often the result of maternal fluid overload in the setting of high-dose tocolytic agents, immobility, and general anesthesia. It can be treated effectively with furosemide, but this must be administered in small incremental doses because uterine contractions will occur if the uterine muscle dehydrates too rapidly in response to a loop diuretic. Oligohydramnios may be due to a slow, occult leak of amniotic fluid from the hysterotomy site into the maternal peritoneal cavity in some patients. The amniotic fluid level may remain low indefinitely until delivery, but in a significant proportion of patients it may increase with spontaneous resealing of the leakage site. Gross rupture of the membranes is usually characterized by a vaginal gush of fluid. Although the likelihood of preterm labor is significantly increased with PPRM, there may be a significant latency period until delivery, and the patient must remain hospitalized under close surveillance for any early signs of infection (chorioamnionitis), which necessitates delivery. In the absence of significant complications, most postoperative hospitalizations last 4 to 5 days.

Preterm labor is by far the most common complication of fetal surgery. The strongest combination of tocolytics (indomethacin and magnesium sulfate) is administered in the first 48 hours following surgery. If mothers are doing well with minimal to no contractions on uterine monitoring, they are transitioned to an oral tocolytic, nifedipine. Because a fresh hysterotomy scar is stretched farther apart every day by a growing fetus, patients must remain on a tocolytic agent until they deliver. Women with a fresh hysterotomy cannot labor because of the high risk for uterine rupture. Therefore, patient education regarding the signs and symptoms of preterm labor and the recognition of abnormal contraction patterns is an essential component of discharge planning. The liberalization of activity from strict bed rest to modified bed rest to light activity depends on the patient's uterine activity.

Once all the postoperative goals have been met (ability to void and tolerate oral intake, adequate pain control, uterine quiescence, normal amniotic fluid volume, reassuring fetal heart rate tracings, postoperative teaching, ability to ambulate to the bathroom, and availability of a companion to assist in the patient's care during activities of daily living), the patient is discharged with a wheelchair and scheduled for weekly follow-up appointments. These will include an ultrasound (assessment of amniotic fluid volume, separation of the chorion and amnion, cervical length, ventricle size, and changes in the Chiari malformation; interval fetal growth can be assessed every 2 weeks), a visit to the obstetrician, and non-stress testing (NST)/antenatal testing.

Patients must deliver at 37 weeks of gestation (if they have not already delivered) because of the increased risk for uterine dehiscence and rupture with the thinning and stretching of the uterine myometrium close to term, as well as the higher likelihood of spontaneous labor. Cesarean delivery is performed via a standard low transverse uterine incision and rarely involves the fetal surgery hysterotomy site. (Proximity to the hysterotomy site, often posterior, fundal, or high, is not practical at the time of term or near-term delivery.) It cannot be overemphasized

that patients, and their primary obstetricians or perinatologists, must understand that they cannot labor in this or any subsequent pregnancy. Because the uterine defect created by the hysterotomy will never be as strong as the native tissue, patients are advised to have a scheduled cesarean delivery at 37 weeks during all future pregnancies. Inability to comply with this requirement is a contraindication to fetal surgery.

22.5.11 Postnatal Considerations

In general, the management of an infant who has undergone fetal repair is the same as that of an infant delivered at full term. A neurologic evaluation and assessment by other teams, such as urology, orthopedics, and pediatrics, are performed. MOMS required postnatal MR imaging, but this may not be required in all cases. Ventricular size at birth should be determined so that it can be followed during the initial hospitalization and after discharge.

In the lumbar region, the fetal repair usually appears well healed, and even if there are small deficiencies in the skin, they usually become covered quickly. Although we generally counsel families that a secondary repair of the skin may be necessary after delivery, this has rarely been the case. In situations in which a dural patch was used during the fetal repair, the patch itself is clearly visible but surrounded by granulation tissue at the time of delivery. During the first 2 weeks after delivery, the granulation tissue usually covers the patch, so that further closure is not required. It seems that the intrauterine environment inhibits epithelialization of the dural patch. If there is leakage of CSF, or separation of the patch, then a postnatal skin repair may be required. This is far more easily done in the postnatal period because the skin is much stronger, and the size of the defect is smaller relative to the size of the back. Before hospital discharge, the infant is referred to a spina bifida clinic for further follow-up care near the family's place of residence.

22.6 Fetal Treatment of Hydrocephalus

Fetal ventriculomegaly is easily diagnosed at 18 weeks, making hydrocephalus potentially treatable with fetal surgery. The fetal treatment of hydrocephalus was first reported in 1981,³⁷ with a number of these procedures performed in the early 1980s. Mechanical failure, complications, and frequent misdiagnosis of associated anomalies led to a voluntary moratorium on these procedures. A fundamental difficulty has been the lack of improvement that seems to be associated with fetal intervention in comparison with postnatal treatment. Several studies examining the treatment of aqueductal stenosis were identified and the results compared with those in the International Fetal Surgery Registry. The rates of survival and normal neurologic outcome were remarkably similar.^{38,39}

Although the clinical experience with fetal shunting is not encouraging, recent advances in fetal imaging, the control of premature labor, and surgical technique may leave this procedure open as an option for highly selected patients. The ideal candidate would have isolated, nongenetic aqueductal stenosis, with progressive ventriculomegaly diagnosed significantly before fetal lung maturity. The experience with fetoscopic fetal surgery

suggests that such an approach would likely be better tolerated than the ultrasound-guided percutaneous techniques used in the past. There are good reasons to be cautious. Since exclusion of associated CNS anomalies that would independently affect outcome might result in very few fetuses being eligible for this type of intervention. At present, this procedure is not being offered at our institution.

22.7 Conclusion

MOMS and pretrial experience demonstrate that fetal surgery for myelomeningocele can be performed safely, with acceptable maternal and fetal risks. Whether these risks are balanced by a benefit to the child over many years is unknown. The impact on other long-term disabilities also remains unknown and will be determined only as groups of patients are followed over time. A team approach is essential if fetal surgery is to be performed successfully.

Pearls

- Based on the results of a randomized prospective clinical trial, potential benefits of fetal surgery for myelomeningocele include reduced rates of shunt placement, and improvement in the Chiari II malformation.
- Maternal risks include premature labor, uterine dehiscence, and a requirement of Cesarean section for all future pregnancies.
- The longterm benefits of fetal intervention are not well understood.

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23 Spinal Meningocele

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Spinal meningoceles are defined as congenital herniations of dura and arachnoid through a bony defect in the spine. Occasionally, nerve roots may be contained within the sac, but the spinal cord is usually normal and is not contained within the sac. There are multiple classifications for spinal dysraphism,¹ the most common of which separates closed lesions from open lesions. Meningocele is considered by some to be a form of closed spinal dysraphism, consisting of skin-covered defects in the vertebral arch. Closed spinal dysraphism is further divided into lesions with a subcutaneous mass and those without a mass. Meningocele usually fall into the former category, along with lipomyelomeningocele and terminal myelocystocele. Anterior and lateral meningocele usually do not have an associated subcutaneous mass because of their location. In contrast to closed spinal dysraphism, open spinal dysraphism includes cystic lesions, which are not entirely skin-covered, such as myelomeningocele, myelocele, and rachischisis.

The true prevalence of spinal meningocele is hard to measure as meningocele are often grouped with myelomeningocele.^{2,3} The total incidence of spina bifida in the United States is 0.3 to 0.4 per 1,000 live births.⁴ Spinal meningocele occur in 1 per 15,000 to 20,000 births and are less common than myelomeningocele, with less than 1 meningocele for every 20 myelomeningocele.⁵ The majority (95%) of meningocele occur in the lumbar spine, and most are skin-covered. Associated hydrocephalus is seen in fewer than 5% of cases. Many meningocele contain associated nerve roots within the sac and are therefore not technically true meningocele as the definition would suggest; rather, they represent an outward pouching of dura associated with a normal spinal cord and nerve roots. Microscopic evaluation can show ganglion cells and glial nodules as an extension from the central canal that may also be contained within the sac.³

23.1 Pathophysiology

The pathophysiology of meningocele depends upon the location and position within the spine. Posterior lumbar and posterior sacral meningocele are thought to occur secondary to defects in secondary neurulation.⁵ Anterior and lateral meningocele occur in association with generalized mesenchymal abnormalities, as may be seen with neurofibromatosis type 1 (NF-1) and Marfan syndrome. In addition, there may be a ball valve effect that results in enlargement of the meningocele sac overtime.

23.2 Classification

The term *meningocele* encompasses a heterogeneous group of mostly congenital lesions that occur adjacent to the spinal column. In the case of posterior spinal meningocele, there is a congenital herniation of dura and cerebrospinal fluid (CSF) through a bony defect in the posterior arch. Posterior meningocele occur most commonly in the lumbar and sacral spine, but they may also occur in the cervical and thoracic spine.⁶ Anterior and lateral spinal meningocele result from generalized mesen-

chymal abnormalities, and although most are congenital, they may progress and be detected postnatally. Posttraumatic or post-procedural meningocele can occur after disruption of the dura but are considered pseudomeningocele. We focus on congenital meningocele in this chapter. For purposes of this discussion, spinal meningocele are categorized based on a posterior or anterior/lateral location as well as on level of the spine (cervical, thoracic, lumbar, or sacral).

23.3 Posterior Meningocele

23.3.1 Lumbar and Sacral Meningocele Presentation

Patients with meningocele usually present after recognition of a skin-covered dorsal mass (► Fig. 23.1) and (► Fig. 23.2). Meningocele may also be diagnosed on prenatal ultrasound, although the detection rate is less than that for open spinal dysraphic lesions because there are no indirect signs such as Chiari 2 malformation (banana sign) and frontal bossing (lemon sign), which may occur with myelomeningocele.⁷ Alpha-fetoprotein levels should be normal with the skin-covered defect, in contrast to the elevated levels present with open spinal dysraphism. The neurologic examination is often normal because most meningocele contain only spinal fluid without neural tissue. However, when they are associated with other anomalies, such as tight filum terminale, tethered cord, hydromyelia, split-cord malformation, and neurenteric cyst, there may be neurologic compromise at presentation.^{8,9} Spinal meningocele may be associated with additional spinal anomalies, so it is important to obtain magnetic resonance (MR) imaging of the entire spine. MR imaging will show a dorsal fluid-filled sac that is hyperintense on T2 sequences (► Fig. 23.3). The entire spine should be evaluated because occult spinal lesions may be present in up to 81% of patients with meningocele.⁹

Differential Diagnosis

The differential diagnosis of a posterior skin-covered cystic lesion includes meningocele, lipomyelomeningocele, myelocystocele, sacrococcygeal teratoma, and pseudomeningocele. Meningocele, in contrast to lipomyelomeningocele, may transilluminate. Sacrococcygeal teratomas are located at the level of the coccyx, more caudally than most meningocele. A pseudomeningocele usually presents after prior surgery or trauma and occurs through an iatrogenic defect rather than a congenital one.

Treatment

Repair of a posterior meningocele is usually recommended at the time of presentation to prevent subsequent tethering, infection, growth of the sac, and CSF leak. Treatment of a meningocele consists of removal of the sac and repair of the defect. Although more than 90% are not associated with neurologic deficits, it is important to perform an intradural exploration and evaluate for any cord tethering before the stalk is



Fig. 23.1 Typical lumbosacral meningocele in a newborn. Overlying skin is normal. The neonate had no neurologic deficit. The meningocele was repaired, and the patient has remained completely normal.



Fig. 23.3 Sagittal T2-weighted magnetic resonance image of a lumbar meningocele.



Fig. 23.2 (a) Newborn with a larger, more pedunculated meningocele in the lumbosacral region. The skin is fully epithelialized, although mildly dysplastic. The patient's neurologic examination was normal and has remained so. (b) After the meningocele dome had been opened, a fibroglioma nodule, densely adherent to the meningocele sac, was noted (*black arrow*) and resected flush with the spinal cord to minimize subsequent tethering. The *white arrow* points to the pedicle where the meningocele connected to the lumbar subarachnoid space.

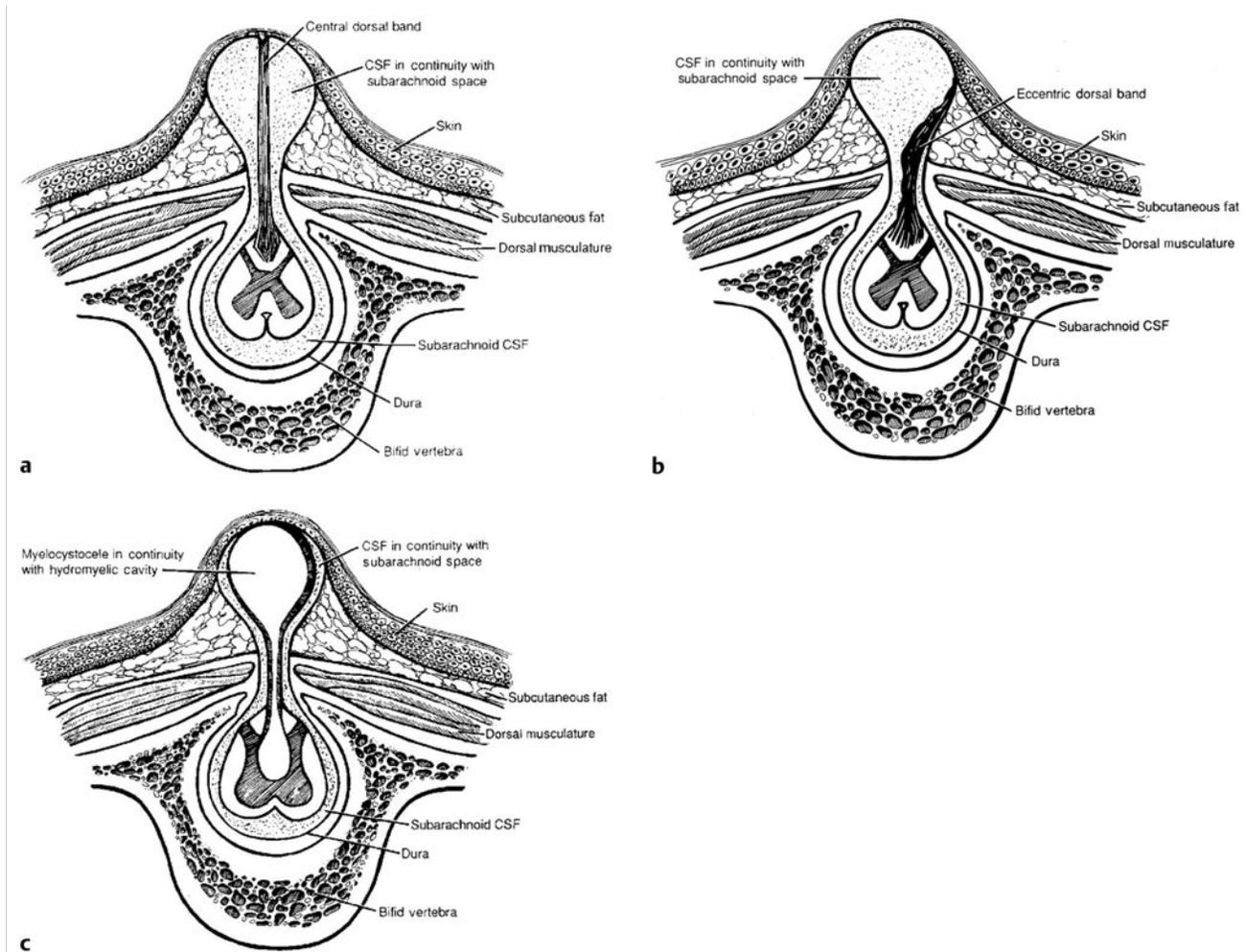


Fig. 23.4 (a) Cervical meningocele with a fibroglial band extending from the dorsal surface of the spinal cord to the dome of the meningocele. (b) Cervical meningocele with a fibroglial stalk eccentrically located and extending from the dorsal surface of the spinal cord to the lateral aspect of the meningocele sac. (c) Cervical meningocele with a hydromyelic central canal herniating from the dorsal surface of the spinal cord to produce a myelocystocele. CSF, cerebrospinal fluid. (Reproduced with permission from Steinbok P, Cochrane D. Cervical meningoceles and myelocystoceles: a unifying hypothesis. *Pediatr Neurosurg* 1995;23:320–321)

amputated⁹ because there may be intradural fibrous bands extending from the spinal cord into the sac. It is occasionally necessary to perform laminectomies and explore one to two levels above and below the lesion for tethering bands. The sac may be ligated and amputated if no neural tissue is present.

Follow-up

If there is clinical concern, patients who undergo surgery for spinal meningoceles may be followed for recurrence of the meningocele or signs and symptoms of subsequent tethering, which may result in weakness, urologic changes, or scoliosis. In some cases, follow-up with MR imaging may be performed.

23.3.2 Cervical Meningocele

Cervical meningoceles are thought to arise from incomplete fusion of the posterior aspect of the neural tube when the cutaneous ectoderm fails to separate from the neuroectoderm.¹⁰ This

results in an abnormal connection of the neural tube to the skin. Cervical meningoceles, myelomeningocele, and myelocystoceles are often grouped together as cervical spinal dysraphism and account for 4 to 8% of patients with spina bifida cystica.¹¹ Cervical meningoceles represent 2% of all meningoceles.¹² There are several theories regarding the embryologic origin of these three entities, with one theory implicating limited dorsal myeloschisis as the underlying abnormality in both meningoceles and myelocystoceles¹⁰ (► Fig. 23.4). In both cases, limited dorsal myeloschisis results in an abnormal attachment of the neuroectoderm to the cutaneous ectoderm. If the central canal does not dilate, it regresses, leaving behind a band of tissue that extends to the dorsal aspect of the meningocele cavity. This band of tissue may contain glial, ependymal, or neural tissue, and its course may be either directly dorsal or lateral to one side of the meningocele sac. If the central canal remains dilated, an associated hydromyelic cavity is created that results in a myelocystocele, which distends and displaces the surrounding subarachnoid meningocele.



Fig. 23.5 Neonate with a cervical meningocele that has a wide base and is covered almost entirely by dysplastic skin. An eschar is noted at its dome (dark area).



Fig. 23.6 Posterior cervical meningocele in an infant.

A more recent classification has been proposed, and as in previous work published on cervical meningoceles, it emphasizes the presence of an intradural stalk in stratifying cervical meningoceles.¹³ This classification separates lesions with a fibrovascular or neuroglial stalk from those without a stalk. Lesions without a stalk are classified as true meningoceles. Therefore, depending on the definition and classification system used, the term *cervical meningocele* may encompass several entities—a true meningocele sac devoid of any neural tissue or a meningocele sac containing a stalk.

Cervical meningoceles usually present as a noticeable midline dorsal cervical mass (► Fig. 23.5) and (► Fig. 23.6). These lesions are usually skin-covered and rarely leak CSF.¹⁴ In contrast to lumbosacral meningoceles, cervical meningoceles may be associated with additional anomalies, such as hydrocephalus, Chiari 1 malformation, hydromyelia, lipomyelomeningocele, split-cord malformation, and Klippel-Feil syndrome.^{8,15,16} This association may reflect the relative heterogeneity of the term *cervical meningocele* because studies that separate meningoceles with hydromyelia (myelocystoceles) from meningoceles without hydromyelia suggest that true meningoceles are rarely associated with additional anomalies, such as hydrocephalus and Chiari 2 malformation.^{14,17} In addition, there are fewer associated anomalies with a true meningocele, according to the alternative classification of Salomão et al.¹³ Nevertheless, because of the association with additional abnormalities of the neuraxis, MR imaging of the brain and entire spine is indicated.^{8,15,18}

It is necessary to repair cervical meningoceles at the time of presentation because tethering by fibrous tissue extending to the dorsal aspect of the meningocele sac may lead to progressive neurologic symptoms over time.¹⁹ Operative repair involves opening the sac and performing intradural exploration for any points of tethering by fibrous bands. Goals of surgery include untethering, resection of the meningocele, cosmesis, creation of a watertight dural closure, and prevention of infection.¹⁹ Long-term follow-up was assessed in one study of four patients with cervical meningoceles.¹¹ Among the three patients with an isolated cervical meningocele, there were no long-term neurologic or urologic abnormalities. Mild orthopedic abnormalities were noted in three patients, none of which required bracing or surgery.

23.3.3 Thoracic Meningocele

Posterior thoracic meningoceles are rare and less common than lumbar or sacral meningoceles.²² In a series of 22 patients presenting with spinal meningoceles, 18% of them were in the thoracic region and 77% were in the lumbosacral region.⁹ Patients may initially present because of a skin-covered dorsal mass or present after birth with radicular pain. There are usually no neurologic deficits. Surgical treatment is similar to that for dorsal meningoceles that occur in other regions of the spine, with the primary goal of evaluating for intradural tethering bands²³ and resecting the meningocele sac.

23.4 Anterior and Lateral Meningocele

23.4.1 Cervical, Thoracic, and Lumbar Meningocele

Meningocele that occur at the anterior or lateral aspect of the spinal column result from a different mechanism than those that occur posteriorly. Anterior and lateral meningoceles are rare and are thought to result from mesenchymal disruptions, as often occurs in NF-1 or Marfan syndrome.^{24,25} These lesions have also been associated with lateral meningocele syndrome and Currarino triad (see later section on anterior sacral meningoceles). Lateral meningoceles that are not associated with either Marfan syndrome or NF-1 may be part of lateral meningocele syndrome,²⁴ which has autosomal-dominant inheritance and is associated with craniofacial abnormalities and connective tissue dysplasia.²⁶ The majority of anterior and lateral meningoceles associated with Marfan syndrome occur in the thoracic or lumbar spine, whereas those associated with NF-1 most often occur in the thoracic spine.²⁴ In the setting of Marfan syndrome, the development of dural ectasia and meningoceles is thought to occur from progressive dilation of the dura secondary to CSF pulsations distending abnormal dura.²⁷ In NF-1, meningoceles may occur secondary to trauma, dural ectasia, cystic degeneration of a neurofibroma, trauma, or congenital

herniation of dura.^{24,28} Their location in the thoracic spine may be secondary to a relatively high pressure differential between the CSF and the thoracic cavity that is due to weak paravertebral muscles.³² Anterior and lateral meningoceles are rare in the cervical spine.²⁴

Unlike posterior meningoceles, anterior and lateral lesions do not have associated skin abnormalities and may present throughout childhood and into adulthood. Growth over time may occur through the intervertebral foramen or anteriorly after erosion of the surrounding vertebral body.³³ Anterior growth may also cause respiratory failure by compression of the lung or trachea. Presentation may occur at any age and may be associated with radicular pain, weakness, respiratory compromise, or neck pain.²⁴ These lesions are often asymptomatic and may be incidental findings on imaging performed for other reasons. MR imaging should always be performed to delineate the lesion and to evaluate for associated compression or other spinal anomalies, such as associated arachnoid cysts, tethering bands, and lipoma. In the case of NF-1, MR imaging may identify a neuroma associated with the meningocele.²⁵ X-ray or computed tomography (CT) may demonstrate widened intervertebral foramina and erosion or scalloping of the vertebral bodies. There is usually no dysraphic laminar defect, as occurs with posterior lesions. On CT, the meningocele will appear hypodense, similar to CSF, and CT myelography will show a communication between the CSF spaces and the meningocele.

Treatment is indicated if a lesion is symptomatic (e.g., neurologic deficit or respiratory compromise). Asymptomatic lesions may be treated conservatively. Anterior or posterior approaches may be used, depending on the location, size, and presence of an associated neuroma.^{24,25} For most laterally directed meningoceles, a posterior approach with intradural repair is preferred. For larger lesions, an extradural lateral extracavitary approach is appropriate. For anterior thoracic lesions, an anterolateral transthoracic approach is recommended to access the lesion. Video-assisted thoracoscopy may also be used. A transthoracic–transdiaphragmatic approach or transpleural–retroperitoneal approach may be used for lesions at the thoracolumbar junction. Other treatments may include a cystopleural shunt.³³

23.4.2 Anterior Sacral Meningoceles

Anterior sacral meningoceles are rare and occur as a CSF-filled dural sac in the presacral space that connects with the spinal canal through an anterior sacral bony defect.³⁴ Most are congenital, and a female predominance has been noted.^{35,36} They are thought to arise from the agenesis of anterior sacral elements.³⁷ Although most often sporadic, anterior sacral meningoceles may display an autosomal-dominant inheritance pattern with variable penetrance.^{38,39} They may also be associated with Currarino syndrome—the triad of anorectal stenosis, sacral bony defect, and presacral mass.⁴⁰ The presacral mass is often a meningocele, teratoma, or epidermoid or dermoid cyst. A recent review of the Currarino triad noted five patients with tethered cord or anterior myelomeningocele,⁴¹ and it is possible that some anterior sacral lesions thought to be meningoceles actually contain nerve roots or neural structures.

Anterior sacral meningoceles may present earlier than anterior and lateral meningoceles in the thoracic spine. A presenta-



Fig. 23.7 Characteristic scimitar deformity of the sacrum seen in anterior sacral meningoceles.

tion with constipation may be due to the direct compression of pelvic structures or secondary to tethering of nerve roots or the spinal cord. Other presenting signs include headaches resulting from intracranial hypotension secondary to CSF accumulation in the meningocele.²⁴ Urinary dysfunction and back or radicular pain are also possible. Female patients may present during pregnancy with dystocia, and in the past, this was a cause of significant mortality due to rupture of the meningocele during delivery.³⁶ Prenatal diagnosis is rare.⁴² There is no cutaneous mass or abnormality; however, a mass may be palpated during an abdominal, a rectal, or a vaginal examination. In any newborn presenting with constipation, a thorough rectal examination should be performed. X-rays may show the classic scimitar sign of the pelvis; this results from a lack of pelvic development on one side, which leaves a contralateral area of bone in the shape of scimitar (► Fig. 23.7). Despite the large bony defect, the neck of the meningocele is often much smaller.^{34,35} MR imaging will differentiate other presacral masses, such as teratomas and epidermoid or dermoid cysts, and will also show a tethered cord if present (► Fig. 23.8). On CT, the meningocele will appear hypodense, similar to CSF. CT myelography will show a communication between the CSF spaces and the meningocele (► Fig. 23.9). As anterior sacral meningoceles may be inherited, some recommend screening immediate family members with a lumbosacral X-ray.³⁸

Anterior sacral meningoceles are generally surgically treated if the patient becomes symptomatic, such as with severe constipation. Incidentally discovered anterior sacral meningoceles can be followed conservatively, although precautions during pregnancy, such as delivery via cesarean section before labor, are advised. Treatment is complex and is usually performed through a posterior approach. Often, functional nerve roots are present along the anterior wall. When possible, ligation of the sac should be performed in symptomatic patients, provided there are no traversing nerve roots through the neck of the sac. If nerve roots are present in the neck of the sac, they should be preserved and the dura approximated around the nerve roots. If spinal cord tethering is present, untethering of the cord should also be performed. A subsequent anterior approach may



Fig. 23.8 T1-weighted sagittal magnetic resonance image showing an anterior sacral meningocele. *Arrow* points to the site of communication. The spinal cord was in a normal location, and the filum terminale was not thickened

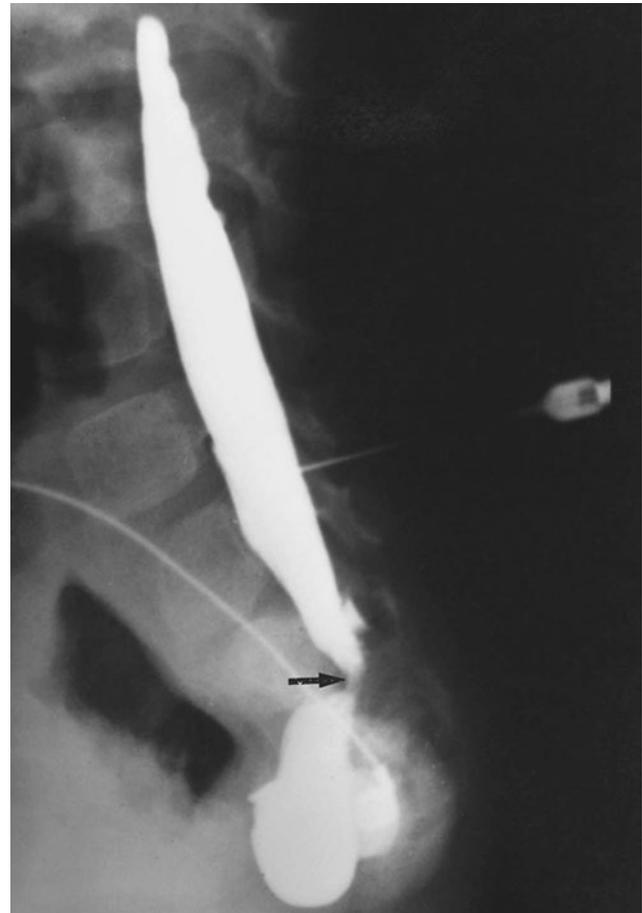


Fig. 23.9 Myelogram showing the connection between the subarachnoid space and the anterior meningocele. Note that the connection is quite small (*black arrow*).

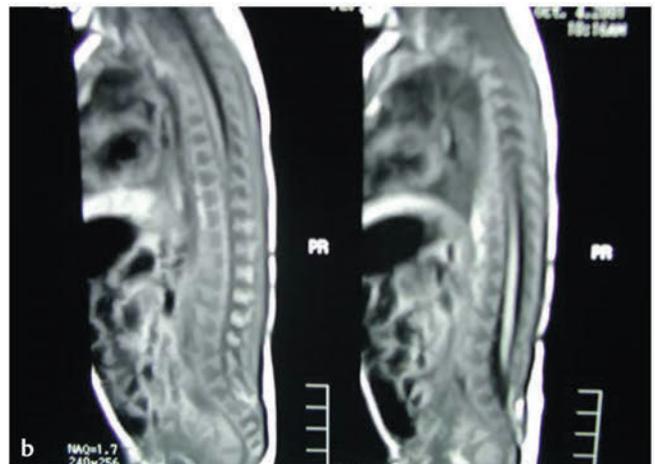


Fig. 23.10 (a) Atretic meningocele in a 9-month-old infant showing the characteristic blue hue. (b) Sagittal T1-weighted magnetic resonance image showing absence of communication between the spinal canal and subcutaneous tissues.

also be necessary, particularly if a diverting colostomy is needed or, in rare cases, if the meningocele is associated with an expanding mass such as a teratoma or an epidermoid or a dermoid cyst. Cyst aspiration alone should not be performed because of the risk for meningitis and failure to treat the underlying abnormality.

The prognosis following repair of an anterior sacral meningocele is good. Follow-up with MR imaging is helpful to demonstrate obliteration of the fistula.

23.5 Meningocele Manqué and Atretic/Rudimentary Meningoceles

A meningocele manqué is a spinal meningocele that initially forms in the embryo but does not develop into a cystic mass. This term was originally introduced by Lassman and James in 1977.⁴³ They described fibrous dorsal bands with or without nerve roots that tethered the spinal cord to the dorsal dura or penetrated through the dura adhering to the lamina. These lesions are associated with a tethered cord in 84% of cases and split cord in 74% of cases. Cutaneous stigmata are present in 68%, the majority in the lumbar spine.⁴⁴ They are often discovered while other dysraphic lesions, such as split-cord malformations, are being treated. The dorsal bands may extend past the dura to the skin, and this should be taken into account when the lesion is accessed because there may be tethering from the skin to the spinal cord.

An atretic or rudimentary meningocele occurs after a spontaneous arrest in the development of a meningocele, where there remains an abnormal attachment of the neural tube to the skin.⁴⁵ A cutaneous outward pouching or cutaneous stigmata remain, and meningotheelial elements are found in the skin and subcutaneous tissues.⁴⁵ There is often a bluish hue to the lesion (► Fig. 23.10a). There may or may not be a bony defect. These patients should undergo MR imaging because there may be a communication with the dura, as in a meningocele. However, imaging is often normal (► Fig. 23.10b).

Pearls

- Patients with meningoceles usually have normal neurologic function.
- Associated hydrocephalus or Chiari 2 malformation is rare.
- MR imaging of the entire spine should be performed at the time of presentation to assess for additional spinal lesions.
- Intradural exploration of the meningocele is necessary to identify any tethering bands.
- Anterior and lateral thoracic meningoceles are often associated with NF-1 or Marfan syndrome and require treatment only if symptomatic.
- Although often sporadic, anterior sacral meningoceles may be inherited or associated with Currarino syndrome.

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24 Myelomeningocele

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Myelomeningocele (MMC) represents a primary failure of neurulation and results in an exposed segment of spinal cord on the back of an infant; MMC is the most severe central nervous system (CNS) malformation compatible with life. Improved nutrition and periconceptional folate supplementation have significantly reduced the incidence of this disorder. Improved treatments, including valved shunt systems for hydrocephalus, surgical treatments for symptomatic Chiari malformations and spinal cord tethering, clean intermittent catheterization (CIC) of the neurogenic bladder, and orthopedic surgical procedures and external orthoses to improve ambulation and mobility, have greatly improved the outlook for these children; many are entering adulthood, and transitional issues have consequently assumed significance. This chapter reviews various facets of MMC in childhood.

24.1 Embryology and Genetics of Myelomeningocele

Open neural tube defects (NTDs), such as MMC and anencephaly, are primarily caused by a localized failure of neurulation,¹ although a few may arise from overdistention of a previously closed neural tube.^{2,3} NTDs in animals have been produced by teratogens (reviewed by Campbell et al⁴), genetic mutations (reviewed by Copp et al^{5,6}), and experimental manipulations (reviewed by Schoenwolf and Smith⁷), although the cause of human malformations remains unknown. NTDs are likely etiologically heterogeneous^{4-6,8} and represent the end result of a variety of embryonic disorders.

The importance of genetic factors is supported by the increased prevalence of NTDs among certain ethnic groups,⁹⁻¹¹ in association with certain genetic syndromes¹²⁻¹⁵ and chromosomal defects,¹⁵⁻¹⁹ and among families with NTDs.^{9-11,20} Over 200 genetic mouse models with NTDs have been identified.^{21,22} Candidate genes are involved in the retention and metabolism of folate²³⁻²⁸ and vitamin B₁₂,²⁹ the methylation cycle and transsulfuration,^{26,28,30,31} glucose transport and metabolism,³² oxidative stress,³³ retinoid metabolism, transcription factors, and DNA repair. Folate (vitamin B₆) is particularly important. Periconceptional folate reduces both the incidence of NTD among women who have not previously had an infant with NTD (400 µg/d) and recurrences among those with a previously affected pregnancy (4,000 µg/d).^{34,35} Folate and its metabolites are involved in purine and pyrimidine synthesis and the transfer of methyl groups during the metabolism of methionine and homocysteine (► Fig. 24.1). Maternal or fetal mutations of enzymes involved in this “methylation cycle” (► Fig. 24.1) may produce methionine deficiency and/or homocysteine excess that can be overcome with supplemental dietary folate.³⁶⁻³⁸ Teratogens like valproic acid disrupt these metabolic pathways.^{38,39} Folate-dependent developmental regulatory genes coding for transcription and cell cycle checkpoint factors may also be involved.

The Chiari 2 malformation is likely an embryologically “acquired” malformation. One theory has proposed that venting of

fluid during early embryonic development causes the formation of a smaller posterior fossa from mesenchyme; subsequent growth of the cerebellum within a small posterior fossa leads to downward and upward displacement of the cerebellum and brainstem, “beaking” of the midbrain, and enlargement of the tentorial notch, as well as disordered neuronal histogenesis resulting in callosal dysgenesis, cortical heterotopias, and stenogyria (see box “Chiari-Associated Central Nervous System Malformations”).⁴⁰⁻⁴² The posterior fossa herniation may be reversible following fetal MMC closure at up to 28 weeks of gestation, although the associated cerebral malformations persist.⁴³

Chiari-Associated Central Nervous System Malformations

- Disorders of the skull
 - Lückenschädel (“skull with gaps”)
 - Small posterior fossa
 - Low-lying tentorium cerebelli with large incisura
 - Scalloping of the petrous bone
 - Shortening of the clivus
 - Enlargement of the foramen magnum
- Disorders of the cerebral hemispheres
 - Polymicrogyria
 - Cortical heterotopias
 - Dysgenesis of the corpus callosum
 - Large massa intermedia
- Disorders of the posterior fossa
 - Descent of the cerebellar vermis through the foramen magnum
 - Caudal displacement of the pons and medulla

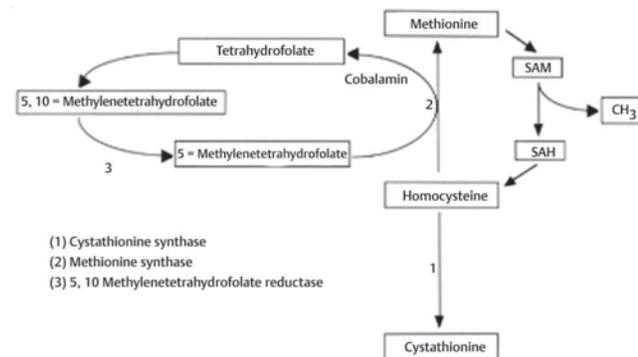


Fig. 24.1 Homocysteine/methionine cycle. The conversion of homocysteine to methionine is mediated by the donation of a methyl group from 5-methyltetrahydrofolate; in the process, tetrahydrofolate is formed. This reaction is catalyzed by the enzyme methionine synthase; cobalamin (vitamin B₁₂) is used as a cofactor. 5-Methyltetrahydrofolate is regenerated from tetrahydrofolate with 5,10-methylenetetrahydrofolate used as an intermediary, completing a “folate cycle.” Methionine is subsequently used as a “methyl (CH₃) donor” in a variety of important metabolic reactions and is converted to homocysteine in the process. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.

- Rostral displacement of superior cerebellum through the tentorium
- “Kinking” of the brainstem
- Loss of pontine flexure
- Aqueductal stenosis or forking
- “Beaking” of the tectum

24.2 Epidemiology of Myelomeningocele, Prenatal Diagnosis, and Counseling

The incidence of MMC is approximately 0.7 to 0.8 per 1,000 live births, with regional variations. The rate in the United States is between 0.3 and 1.43 per 1,000 live births^{44,45} and is lower among African Americans than Caucasians. The incidence of MMC has declined⁴⁶ because of improved maternal nutrition, folate supplementation, elective terminations, and other unknown factors. In the United States, the rate dropped from 0.6 to 0.3 per 1,000 live births between 1984 and 1992,⁴⁴ with little additional decline as of 2004.⁴⁷ The recurrence risk is 1 to 2% among parents having a single previously affected child,^{4,46} and 10% for those having two previously affected offspring.⁴⁸ A woman with MMC has a 3% risk of bearing an affected child.⁴

Although these are most often isolated malformations, autosomal-dominant, autosomal-recessive, and X-linked-recessive transmissions exist.⁴⁹ On the other hand, one study demonstrated a low concordance rate between monozygotic twins.⁵⁰ Human NTDs are likely polygenic.

24.2.1 Prenatal Diagnosis

Maternal serum alpha fetoprotein screening is performed at 16 to 18 weeks of gestation and is 75% sensitive for detecting open

NTDs (anencephaly and/or MMC).⁵¹ Underestimated gestational age, multiple pregnancies, and other fetal disorders, such as omphaloceles, can produce false-positive results; closed, skin-covered spinal malformations, such as myelocystoceles, may also be missed. Fetal ultrasound confirms the diagnosis with a sensitivity approaching 100% in recent series.⁵¹ Direct visualization of the placode and bony abnormalities, or indirect cranial signs such as the “lemon” and “banana” signs (► Fig. 24.2a,b) may be seen; the lemon sign has a sensitivity of 80% and the banana sign a sensitivity of 93%, with a false-positive rate of 0.88%.⁵¹ Amniotic alpha fetoprotein, acetylcholinesterase, and chromosomal analysis may be obtained via amniocentesis. Amniotic alpha fetoprotein levels are elevated in 97% of patients with NTDs,⁵² but acetylcholinesterase measurements are 14% more sensitive than alpha fetoprotein.⁵¹ False-positive elevations of both may occur with fetal blood contamination during sampling, impending fetal death or autolysis, and fetal abdominal wall defects⁵¹; false-negatives are seen with skin covered malformations.

24.2.2 Prenatal Counseling

Prenatal counseling should deliver *accurate information* upon which parents can make *informed decisions*. Almost all children survive with proper treatment^{53,54}; deaths in infancy are most commonly caused by the Chiari malformation and in later life by unrecognized shunt malfunction. The overall long-term mortality is between 24 and 60%, with a mortality of between 15 and 34% in the first 5 years and of 9 to 26% thereafter.^{55,56}

A normal IQ is attained by 70 to 75%^{56,57}; some studies suggest a lower IQ for those with hydrocephalus.^{58–66} Sixty percent of those with a normal IQ have learning disabilities,^{60,67,68} Despite many challenges, 82% of adults are independent in activities of daily living and 30% attend or have finished college, but only 32% are gainfully employed.⁶⁹ Achievement in one study

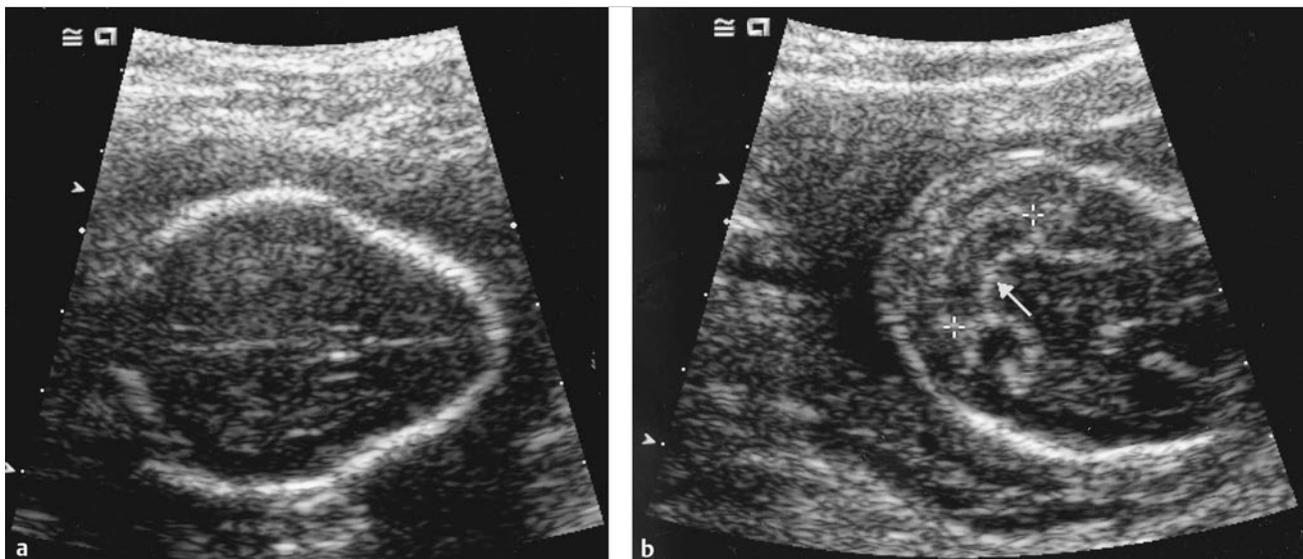


Fig. 24.2 Prenatal cranial ultrasound signs associated with myelomeningocele. (a) Lemon sign (convex inward frontal bones). (b) Banana sign (Chiari malformation).

was attained by 89% of those who never had a shunt placed, 69% of those with shunts but no revisions, 50% of those with shunt revisions before 2 years of age, and 18% of those having shunt revisions beyond 2 years of age.⁶⁵

Ambulation correlates with sensorimotor level.⁷⁰ Excluding 13% with severe delays, 89% of preadolescent children are community ambulators, including most with lumbosacral lesions and 63% of those with upper lumbar lesions.⁶⁷ Ambulation falls to below 50% in adolescence as wheelchair use becomes more efficient.⁵⁸ Few patients with lesions at L3 or a higher level are functional long-term ambulators.⁷¹

Urinary social continence (in social situations) is achieved in about 80 to 85% of school-age children.^{53,56,72-74} CIC is reported in 85%.⁵⁶ Complete bowel continence is achieved in 50% of patients, and almost 90% report continence 75% or more of the time.⁵⁶ About two-thirds of boys report at least some genital sensation, and 70 to 75% achieve reflex erections.

Approximately 70% of children require a ventricular shunt.^{53,58,67} Shunt malfunction occurs in 30 to 40% within 1 year, 60% within 5 years, and 85% within 10 years,^{58,75} and shunt infection occurs in 11 to 26%.⁷⁶⁻⁷⁸ One-third of children will undergo a tethered cord release, 15 to 33% a Chiari decompression, and 1 to 5% an operation for syringomyelia. Orthopedic and urologic procedures are also frequently required.

Cervicothoracic MMCs deserve special mention because the prognosis for sensorimotor function in these children is not predicted by their anatomical level. Most have no identifiable sensorimotor abnormalities at birth, although subtle impairments may become apparent over time; most develop hydrocephalus. Fetal magnetic resonance (MR) imaging is recommended before parents are counseled, especially if termination is being considered.⁷⁹

The best mode of delivery is not clear; studies have produced conflicting results.⁸⁰⁻⁸⁸ Although two nonrandomized studies showed better outcomes following cesarian delivery,^{80,82} five other nonrandomized studies showed no consistent benefit to cesarian over vaginal delivery except perhaps in cases with a breech presentation or significant hydrocephalus.^{81,84-87} Finally, parents should be counseled about the increased risk for MMC with subsequent pregnancies and the need for periconceptional folate (4,000 µg of folate daily, 10 times the amount recommended for the general population).³⁵

24.3 Neurosurgical Management of Children with Myelomeningocele

Given the complexity of MMC, some have thought it more merciful to withhold treatment and allow these infants to die. In 1971, Lorber developed criteria to select infants for nontreatment; these included severe hydrocephalus at birth, total paraplegia, spinal kyphosis, and an additional birth defect.⁸⁹ In 2001, the Groningen Protocol was developed in the Netherlands to select infants for active euthanasia who were thought to be in “unbearable suffering” and to have a “hopeless prognosis”; 22 infants were euthanized by lethal injection as of 2010.

However, none of these criteria, either in isolation or in combination, are entirely accurate predictors of outcome,⁹⁰ and in the United States, most children are treated. In a landmark study by McLone, the outcome of nonselective treatment

compared favorably with that in the selected series of Lorber.⁹¹ Parents of children with MMC in the United States rarely regret a decision to treat their child, with only 4 of 300 regretting their decision to treat and 9 regretting their initial decision not to treat.⁹⁰ Withholding treatment may rarely be considered for children with other, potentially fatal congenital malformations or chromosomal abnormalities, but this decision should be individualized and made only after a frank and realistic discussion with parents.

Neurosurgical care for the child with MMC can be divided into three phases: (1) initial stabilization of the infant and closure of the MMC; (2) assessment and treatment of associated hydrocephalus when present; and (3) long-term management of associated shunt malfunctions, the Chiari malformation, tethered spinal cord, and syringomyelia.

24.3.1 Stabilizing the Infant and Closing the Myelomeningocele

The MMC contains potentially functional tissue, so it should be protected from external mechanical trauma and desiccation and kept as clean as possible. Sterile saline-soaked gauze dressings and plastic wrap keep the malformation moist; iodine-containing compounds should be avoided as they may injure exposed tissues. Prophylactic antibiotics (usually ampicillin and gentamicin) are usually administered for the first 3 days.

The initial newborn evaluation should focus on several aspects. A general physical examination may disclose evidence of a more widespread genetic or developmental syndrome. Sensorimotor function is assessed by observing spontaneous leg movements and the response to pinprick stimulation (► Table 24.1). Muscle imbalance yields characteristic leg postures, such as hip flexion for upper lumbar level lesions, knee extension for midlumbar lesions, and ankle dorsiflexion with low lumbar level lesions. Clinical signs of hydrocephalus include accelerated head growth, full fontanel, split cranial sutures, and limitation of upgaze/“setting sun” eyes. Brainstem signs include bradycardia, apnea, dysfunctional swallow, high-pitched or weak cry, vocal cord palsies, and hypotonia. Severe brainstem dysfunction on the first day of life is a particularly ominous sign, especially if it persists after ventricular shunting.

The MMC may be repaired within the first 3 days without an increased complication risk.⁹² The placode is sharply dissected from the surrounding skin at the perimeter of the malformation

Table 24.1 Assessment of neurologic level in patients with myelomeningocele

Level	Last intact motor level	Sensory level
T10	Rectus abdominis	Umbilicus
L1	Hip flexion	Anterolateral thigh
L2	Hip adduction	Anteromedial thigh
L3	Knee extension	Knee, anterior shin
L4	Foot dorsiflexion	Dorsum of foot
L5	Extensor hallucis longus	First–second interspace
S1	Plantar flexion	Plantar aspect of foot

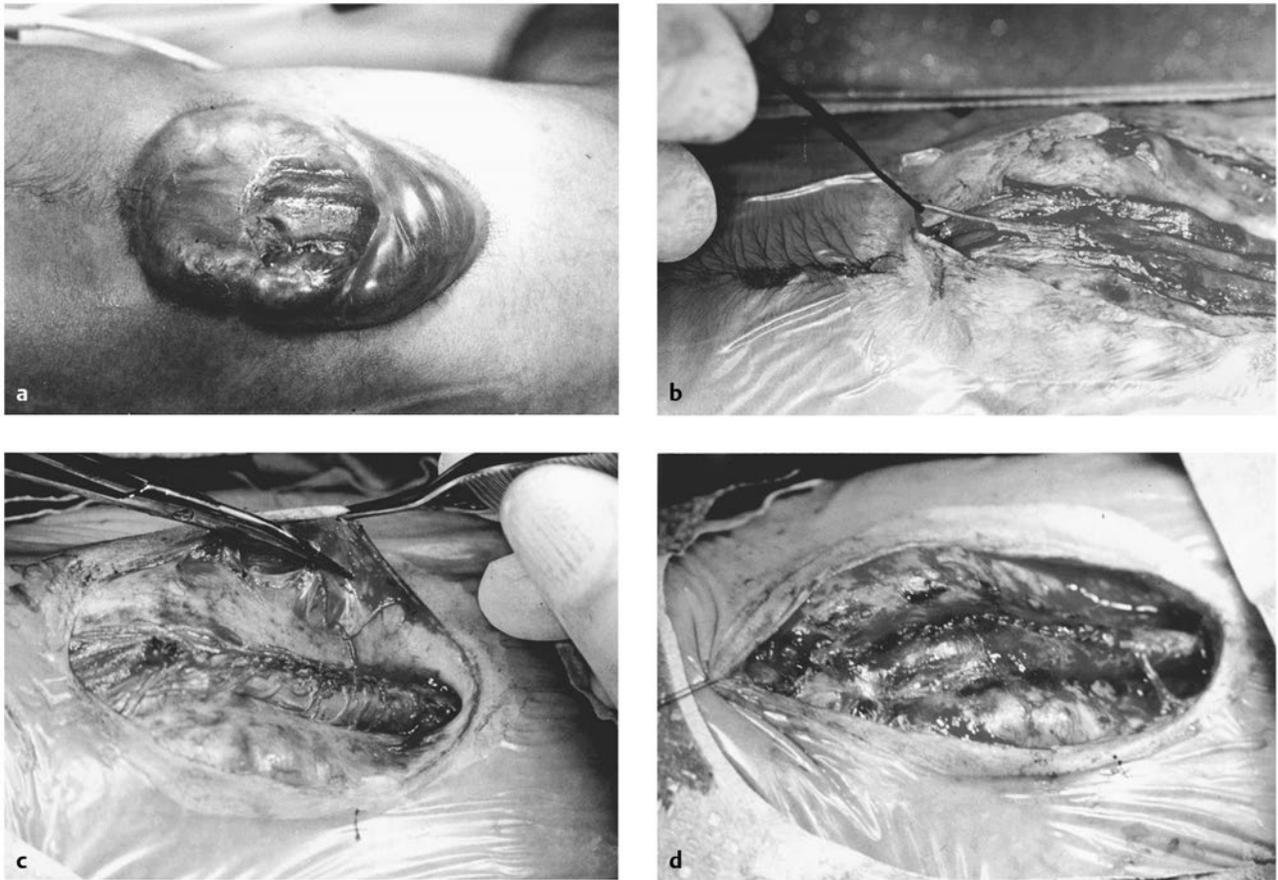


Fig. 24.3 Closure of myelomeningocele. (a) Myelomeningocele sac on dorsum of newborn infant. Placode is in the center and attached circumferentially to the adjacent dysplastic skin. (b) The placode has been dissected circumferentially from the skin and rolled up to re-create a neural tube. In this case, there is an intact filum terminale caudal to the placode, which will be sectioned. (c) The dura is dissected from under the skin circumferentially and brought together to cover the newly “closed” placode. (d) The dura is closed with running suture. The skin is undermined just above the lumbodorsal fascia and brought together in the midline with as little tension as possible. Another layer may be added by elevating the muscles and fascia on either side of the splayed posterior elements and bringing them together over the closed dura before skin closure.

(► Fig. 24.3a), avoiding injury to subjacent nerve roots. Skin tissue is meticulously dissected from the placode to avoid a subsequent inclusion dermoid.^{93,94} Small feeding arteries and draining veins are spared if possible. The lateral edges of the placode are approximated with the use of fine suture to reconstitute the neural tube (► Fig. 24.3c), which may make subsequent untethering easier to perform. Some surgeons excise the placode in patients with thoracic or thoracolumbar lesions and no leg function to facilitate dural closure and reduce the risk for subsequent retethering, but urologic worsening may occur in 8%.^{95,96}

Any other tethering malformation, such as a lipoma, split-cord malformation, or filum terminale, should be untethered if present (► Fig. 24.3b). One important variant, a *hemimyelomeningocele*, is suggested preoperatively by a significantly asymmetric motor examination and a sac that is slightly off midline. A hemimyelomeningocele is a form of split-cord malformation in which the spinal cord splits into two “hemicords,” one of which is exposed on the surface while the other is hidden under, and separated from, the exposed hemicord within its own separate dural sac.⁹⁷

Once the placode is closed and all related tethering malformations treated, the surrounding dura is then circumferentially elevated from the underlying fascia (► Fig. 24.3c), and the dural sac is reconstituted with enough space to avoid strangulating the placode (► Fig. 24.3d). Dural grafts are rarely necessary, do not appear to decrease the risk for subsequent tethering, and may increase the risk for CSF leak.

The lumbodorsal fascia may be closed as an additional layer, but the benefits are unclear as cerebrospinal fluid (CSF) leaks occur in only 1 to 3% overall.⁹⁸ One study found no additional benefit to myofascial closure,⁵⁴ whereas a second study reported that CSF leakage and shunting were less frequent.⁹⁹ Periosteal “turnover flaps” with the use of lumbodorsal fascia and acellular dermal matrix are also reported.^{100,101}

Finally, the redundant skin is trimmed and closed. Vertical, horizontal, and Z-plasty closure techniques¹⁰² have been described, although a simple vertical closure is preferred because it simplifies later spine procedures should they become necessary. The skin is undermined circumferentially above the lumbodorsal fascia with sharp dissection; small perforating vessels

arising from the fascia should be avoided if possible to prevent flap ischemia. As the skin edges are drawn together, some temporarily blanching often occurs but is usually transient; topical nitroglycerin paste may improve skin blood flow. Excess dysplastic skin is trimmed, and the normal skin is closed in a layered fashion.

Large skin defects may require rotational or myocutaneous flaps that are beyond the scope of this chapter and are reviewed elsewhere.¹⁰³ Wound complication rates are lower following flap closure in some studies,^{104,105} but not others.¹⁰⁶ In a novel technique (Ken Winston, personal communication, 1997), Silastic sheeting (used for creating silos for gastroschisis) is sewn circumferentially to the underside of the elevated skin flaps well back from the skin edges. The Silastic sheet is then plicated by drawing up the center of the sheet and suturing it every

other day on the ward to progressively pull the flaps together; once the skin is overlapping, the Silastic sheet is removed and the wound closed primarily (► Fig. 24.4a,b). A similar progressive purse string cerclage technique has also been reported.¹⁰⁷

Severe kyphosis complicates about 12% of cases of MMC.¹⁰⁸ Although most patients are paraplegic, a few have some preserved sensorimotor function. Kyphosis can lead to difficulty with the initial MMC closure, subsequent skin breakdown or ulceration, sitting imbalance, pulmonary restriction, and loss of neurologic function. Kyphectomy at the time of initial closure has been recommended because kyphosis commonly progresses, and later correction is risky. Kyphectomy in infancy significantly decreases recurrence, particularly if the lordotic curvature is restored.¹⁰⁹ The placode is excised and the superior dura imbricated, or the placode and thecal sac are displaced

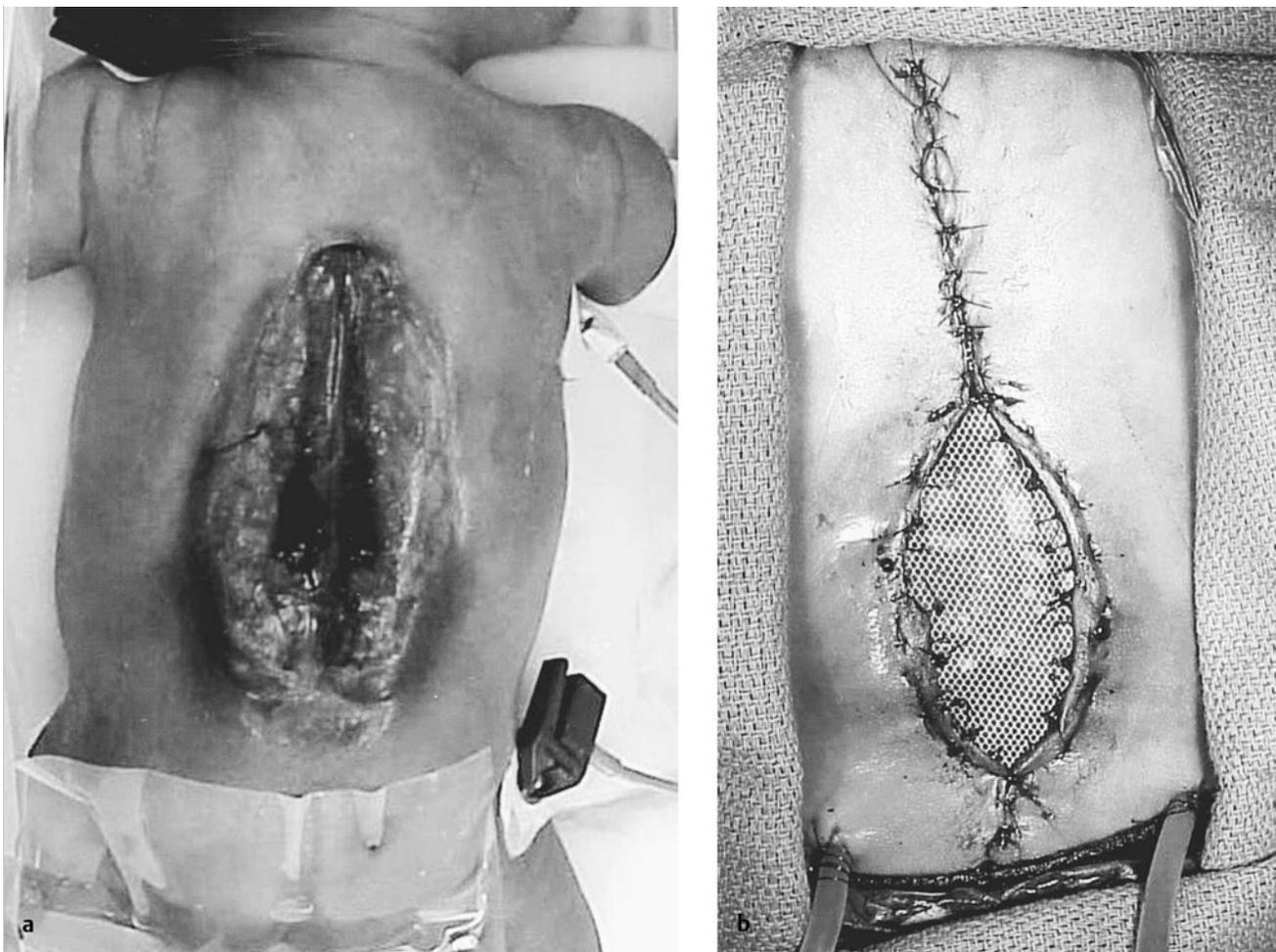


Fig. 24.4 Closure of large myelomeningocele by the progressive approximation of Silastic sheeting. (a) Huge thoracolumbar myelomeningocele. (b) Much of the myelomeningocele has been closed primarily, but the portion that remains open is attached along its undersurface to Silastic sheeting. This sheeting is plicated in the midline every few days in the neonatal intensive care unit, with the skin edges drawn progressively closer until they overlap. The child is then returned to the operating room, the Silastic sheet is removed, and the skin is closed primarily.

laterally to expose the underlying vertebra(e) at the apex of the kyphos. Laterally displaced laminae and pedicles are removed with rongeurs. The vertebral bodies and adjacent disks at the apex of the kyphotic deformity are removed piecemeal with rongeurs and/or a high-speed drill, with extreme care taken to avoid injury to the subjacent vascular and retroperitoneal structures. Hemostasis is meticulous, but a transfusion should be anticipated. The kyphos is reduced by extending the femora under the drapes and bringing the adjacent end plates together; the newly approximated vertebrae are sutured together with several heavy (No. 1 or No. 2) nonabsorbable sutures supplemented with the excised bone chips.¹⁰⁹ A body cast or custom orthosis is worn for 12 weeks.

24.3.2 Initial Treatment of Hydrocephalus

Hydrocephalus occurs in 80 to 90% of children with MMC,^{58,110} and 70 to 90% undergo shunting.^{56,111} For infants with overt signs of hydrocephalus at birth, MMC closure and contemporaneous shunting may be performed with no apparent increased risk and perhaps decreased wound leakage.^{112–114} External ventricular drainage or a ventricular reservoir may be used to temporize, particularly for those infants whose MMC was repaired more than 72 hours after delivery, in whom contemporaneous shunting is associated with a higher infection rate.¹¹⁵

For those with modest ventricular enlargement and no clinical evidence of hydrocephalus, neither absolute criteria nor consensus is available about when to place a shunt. One study suggested that infants with a cortical mantle thickness of 2.8 cm or larger may not need shunting.¹¹⁶ Various measurements, such as the Evans ratio or the average of the maximum frontal and occipital horn widths divided by the distance between the cortical surfaces,¹¹⁷ have been proposed but are rarely used in decision making. There is significant variability among pediatric neurosurgeons regarding the threshold for shunt placement in asymptomatic children with ventriculomegaly,¹¹⁸ likely related to uncertainty about the effects of moderate ventriculomegaly on brain development compared with the risks of shunt revisions and infections. Many pediatric neurosurgeons prefer moderate ventriculomegaly to ongoing and repeated shunt complications.¹¹⁸ On the other hand, cognitive improvements may occur even when a shunt is placed years later.¹¹⁹

24.3.3 Long-term Neurosurgical Management of Children with Myelomeningocele

Children with MMC are best managed in the setting of a multidisciplinary clinic specializing in the treatment of spina bifida, where pediatric surgical specialists, therapists, and a nurse coordinator are available¹²⁰; the clinic can be an integral part of the medical home for these children.¹²¹ Pediatric neurosurgical care focuses on four major issues: the shunt, the Chiari malformation, syringomyelia, and spinal cord tethering. Management follows seven basic principles:

1. Each child has a unique set of *static* neurologic, orthopedic, and urologic deficits.

2. Each child has a set of radiographic abnormalities, including hydrocephalus in 70 to 80%, Chiari malformation in more than 95%, syringomyelia in 40 to 80%, and tethering in virtually 100%.
3. *The mere presence of a radiographic abnormality, or even a radiographic change, does not necessarily direct treatment. Rather, treatment should generally be reserved for clinical deterioration.*
4. *Any neurologic, urologic, or orthopedic deterioration* should prompt a search for a treatable cause.
5. *Any clinical deterioration* can potentially be caused by shunt malfunction, and all evaluations should therefore begin by excluding *shunt malfunction*.
6. If available, ventricular size at the time of suspected shunt malfunction *must be compared with a baseline*. Moreover, a shunt malfunction may occur with *little or no change in ventricular size*. An open mind is required.
7. Papilledema may occasionally develop with few or no symptoms; a *funduscopy examination* should be performed once the child is able to cooperate.

Shunt Management in Children with Hydrocephalus

The signs and symptoms of shunt malfunction in the child with an MMC are legion. The usual symptoms and signs—headache, nausea and vomiting, poor feeding, listlessness or lethargy, setting sun eyes, and extraocular abduction palsies—are not universal. Symptoms may be subtle or intermittent in nature, and of course not every headache is shunt-related. Experienced parents may be able to tell whether or not their child's symptoms suggest shunt malfunction¹²²; be wary of dismissing an experienced parent's concerns! Other patterns of shunt malfunction include the following:

- Cognitive changes such as a decline in school performance or worsening behavior
- New onset of seizures or change in the pattern of seizures without another cause
- Decreased arm or leg strength, loss of previously acquired motor skills, or increased tone
- Unexplained change in ambulation
- Worsening urinary and/or bowel function
- Neck pain, lower cranial nerve or brainstem dysfunction.
- Pain at the MMC closure site
- Progressive scoliosis or orthopedic deformities

Any deterioration should first prompt a thorough investigation of shunt function before any other neurosurgical treatment is undertaken, especially if there are any associated headaches or cognitive changes.

Most children have increased ventricular size on computed tomography (CT) compared with their baseline. A shunt series may reveal disconnected or broken tubing. Notably, shunt pumping is of no demonstrated value.^{123,124} Other adjunctive measures may include a shunt tap, radionuclide study, or continuous intracranial pressure (ICP) monitoring. A shunt tap may be helpful if it demonstrates (1) sluggish or absent proximal flow (suggesting a proximal occlusion), (2) brisk flow and high pressure with manometry (suggesting a distal occlusion), or (3) proximate relief of headaches after fluid removal. Radionuclide

shunt studies involve injecting tracer through the shunt into the ventricles while occluding distal outflow. Over time, the tracer should flow distally; failure to do so suggests malfunction. ICP monitoring is helpful if it demonstrates an acute rise in ICP concurrent with headaches. Unfortunately, shunt taps, radionuclide studies, and ICP monitoring are *least* reliable with a partially occluded shunt, and no test can absolutely exclude a shunt malfunction. Ultimately, the diagnosis rests on the *clinical condition of the child*, and a shunt exploration may be needed if symptoms continue. This cannot be overemphasized—nowhere else in pediatric neurosurgery is clinical judgment so important, and misjudgment so treacherous.

Endoscopic third ventriculostomy (ETV) has emerged as an alternative to shunt revision with overall success rates of higher than 70% among eligible patients with MMC and (1) evidence of noncommunicating hydrocephalus by CT ventriculography and/or MR imaging, (2) minimal or no discernible subarachnoid space, and (3) a third ventricle at least 4 mm wide.¹²⁵ The success rates are lower in children younger than 6 months than in older children.¹²⁵ ETV is technically more challenging and difficult in this population because of abnormal third ventricular anatomy, distorted foramina of Monro, and interthalamic adhesions. A combination of ETV and choroid plexus cauterization (ETV/CPC) was more successful (76%) among infants with MMC in sub-Saharan Africa than was ETV alone (35%), with comparable intellectual outcomes and fewer later failures.^{126,127} Whether these results can be reproduced remains to be seen.

Can a child with MMC and hydrocephalus managed with a shunt ever be considered shunt-independent? There are certainly anecdotes of shunt disconnections or breaks seen incidentally on radiographs in asymptomatic patients. However, abrupt or even fatal deterioration has been reported months or years later.^{128–130} A radionuclide study may confirm that CSF is not flowing through the intervening shunt tract,¹³¹ but the validity of this technique has not been evaluated in patients with MMC. The difficulty in determining shunt independence with certainty, and the possibility of sudden decompensation, should be carefully discussed if observation is chosen.

Management of the Chiari Malformation

The Chiari 2 malformation is a pancerebral abnormality (see box “Chiari-Associated Central Nervous System Malformations”) that is present in most children with MMC. Herniation of the cerebellar vermis, brainstem, and fourth ventricle through the foramen magnum may cause lower brainstem signs and symptoms, although most children are relatively asymptomatic and fewer than one-third require surgery.^{58,91,132–137} Presenting symptoms are most frequent during the first year, with lower cranial neuropathies, swallowing dysfunction, and disordered breathing predominating.¹³² Almost all children with MMC have modest swallowing issues, such as a hyperactive gag reflex, intolerance for particular food textures, gagging (usually on solids), and more frequent vomiting, all of which usually improve over time and do not require treatment. More concerning are *progressive* swallowing abnormalities, such as choking on liquids, significant weight loss, nasal regurgitation, and aspiration pneumonia. Other concerning signs may include those of disordered breathing: central or obstructive apnea, cyanotic spells (sometimes even when the child is on a ventilator¹³³),

inspiratory stridor, and a hoarse, weak, or high-pitched cry. Stridor and apnea at delivery are more ominous and have a higher mortality rate and poorer outcome than stridor and apnea that develop later.¹³⁸ Vocal cord palsies, particularly when bilateral, are often irreversible and require tracheostomy.¹³⁹ Other signs and symptoms (particularly in the older child) may include weakness and/or spasticity of the upper extremities, pain (headache and/or neck pain), cerebellar problems, oculomotor dysfunction, and scoliosis.^{42,132,139,140}

The Chiari 2 malformation is well seen on sagittal T1 or T2 MR images (► Fig. 24.5). A speech and swallow evaluation may disclose phonation difficulties, hoarseness, or abnormal swallow. A formal swallowing study¹³² may disclose disordered swallowing mechanics, incomplete clearing or pooling of tracer in the vallecula, occult tracheal aspiration, or reflux. Radionuclide swallow studies may also reveal occult aspiration. Direct laryngoscopy may disclose unilateral or bilateral vocal cord weakness, and pulmonary studies may demonstrate episodic central or obstructive apnea.

Whether to treat the Chiari malformation depends upon the age of the patient and the severity and progression of clinical signs. Mild, nonprogressive swallowing issues usually improve without treatment. Newborns with apnea, bilateral vocal cord palsies, absent gag or swallowing function, and hypotonia do poorly despite treatment^{138–140} and may have an anatomically disordered brainstem.¹⁴¹ Some argue that Chiari decompression in infants is futile because the high case mortality rate with surgical treatment in infants is no better than the natural history.^{135,142} Others have reported significantly better outcomes in symptomatic newborns who are treated early and aggressively.^{139,140,143} Two studies of symptomatic neonates who underwent early surgery demonstrated significant improvement in 61 to 77%, with better outcomes following earlier treatment but an overall case mortality of 23%.^{139,140} There appears to be little consensus regarding the most appropriate treatment.¹⁴⁴ Older children with symptomatic Chiari 2 malformations have much better postoperative outcomes, although surgery for this population has declined significantly with the realization that most of these patients have an underlying shunt malfunction. The first approach to treating a symptomatic Chiari malformation at any age is to exclude hydrocephalus and/or shunt malfunction, and a shunt insertion or revision should be strongly considered before a Chiari decompression is undertaken.

Chiari decompression involves a cervical laminectomy to the lowest level of the cerebellar tonsils (not to the medullary kink) and duraplasty with autologous tissue or allograft. The foramen magnum is usually large, and occipital bony decompression and posterior fossa dural opening are rarely necessary, entail a greater risk for hemorrhage from intradural venous lakes and pathologically low venous sinuses, and may not improve outcomes. Other procedures, such as opening and/or stenting the fourth ventricle¹⁴⁵ and plugging the obex,^{146–148} are of no proven additional benefit and add considerable surgical risk resulting from dissection through the scarred vermis. Significant syringobulbia may require opening the fourth ventricle and draining the brainstem cyst.

Complications of Chiari decompression are age-related, with the highest mortality rate in infants.^{139,140} Bleeding from dural venous lakes, low-lying transverse sinuses, or the torcular may

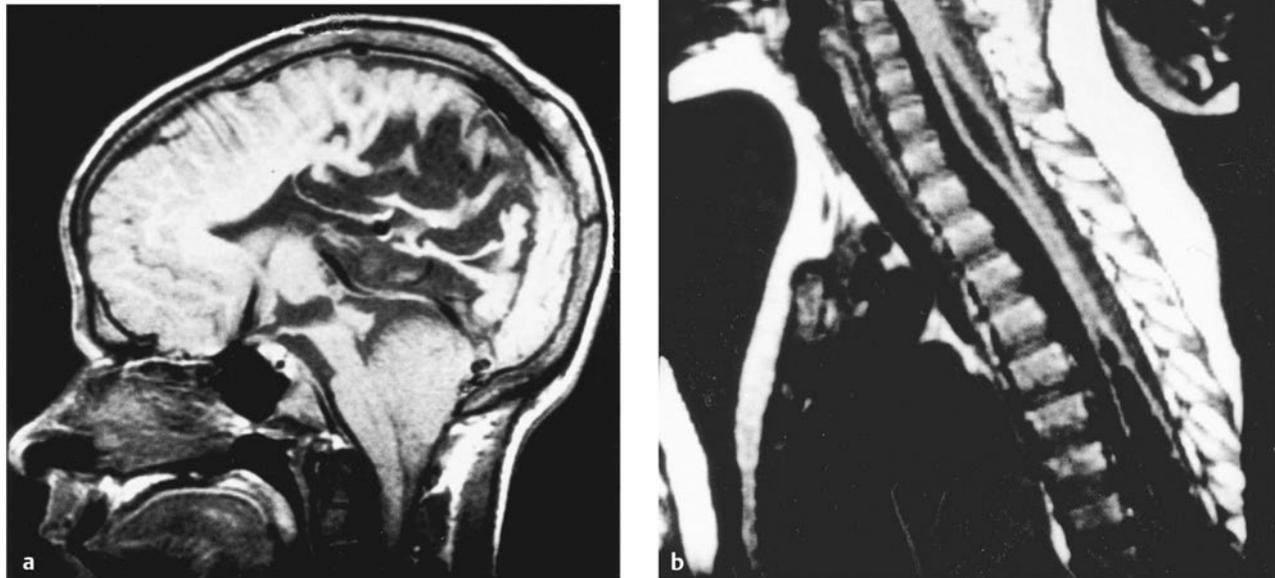


Fig. 24.5 Chiari 2 malformation and syringomyelia. (a) Midsagittal T1-weighted magnetic resonance (MR) image shows disordered sulcation of the posterior cortex (stenogyria), dysgenesis of the corpus callosum, beaked tectum, and enlarged massa intermedia of the thalamus. The cerebellar vermis and brainstem lie below the foramen magnum. (b) Midsagittal T1-weighted MR image showing descent of the cerebellar vermis and brainstem below the foramen magnum and two syringes in the midcervical and thoracic regions.

be frighteningly significant, and the sagittal MR image should be scrutinized preoperatively. Direct brainstem trauma, vascular injuries, CSF leaks, and wound and shunt infections are rare. Delayed post-laminectomy kyphosis is unusual, although one study reported a 40% incidence.¹⁴⁹

The outcome depends upon the age and mode of presentation. Newborns with bilateral vocal cord palsies and apnea often require tracheostomy, gastrostomy, and Nissen fundoplication. Neonates with less severe brainstem involvement and at least one functioning vocal cord¹³⁹ and older children fare better.

Management of the Tethered Spinal Cord

Neurologic deterioration usually has a cause and is not the “natural history of MMC.” Tethering is a well-recognized cause of deterioration in this population,^{150–157} with one-third requiring untethering in childhood.¹⁵⁴ The pathophysiology of tethering reflects physical spinal cord stretching that leads to decreased spinal cord blood flow, a shift to anaerobic metabolism, reduced glucose metabolism, and mitochondrial failure.^{158,159} Vertebral column growth progressively stretches the spinal cord; the incidence of symptomatic tethering increases during periods of

rapid growth.^{151,160–162} Repetitive traction on an already tethered spinal cord with flexion movements of the pelvis and/or spine may exacerbate the problem.¹⁶³ Several studies have documented stabilized or improved neurologic function,^{151,155,160,164–166} urologic function,¹⁵² and orthopedic deformities^{153,156,157} after untethering.

Because every patient with MMC is radiographically tethered (► Fig. 24.6), the decision to untether the spinal cord in this population is based solely upon *clinical grounds*. The position of the conus medullaris does not change appreciably after tethered cord release, even though patients improve clinically.¹⁶⁷ A vigilant eye, keen clinical judgment, and objective, accurate, and reproducible adjuncts, such as serial manual muscle testing, urodynamics, and scoliosis X-rays, are needed to properly evaluate the child for tethering.

Signs and symptoms of spinal cord tethering may include the following:

- Pain in either the back or legs
- Motor deterioration—decreased muscle strength and/or increased tone (spasticity)
- Sensory worsening

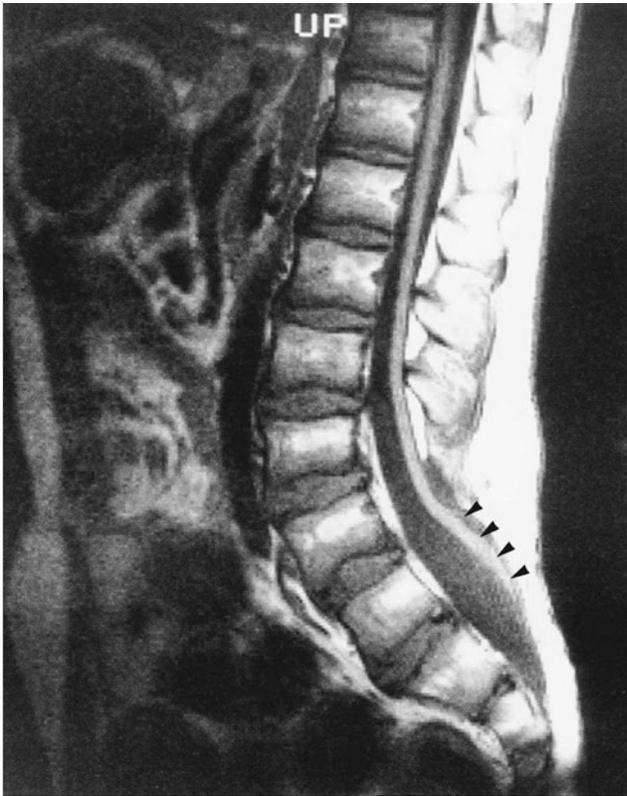


Fig. 24.6 Tethered spinal cord. Midsagittal T1-weighted magnetic resonance image showing the spinal cord ending dorsally at the level of the L4–S1 vertebral bodies (arrowheads).

- Worsening bowel and bladder function
- Deteriorating gait
- Progressive orthopedic deformities of the legs (hip dislocation, pes cavus, equinovarus) or spine (scoliosis)

Pain is common but seldom the only complaint. Pain in the back and/or legs is usually ill-defined, dull, and achy in character, and it may extend even into areas that are insensate. Leg pain may have a dysesthetic or neuropathic quality and be exacerbated by exercise or effort. Fortunately, pain is almost universally relieved after untethering procedures.

Sensorimotor changes are the most frequent presentation¹⁶⁸ and include declining muscle strength, increased tone (spasticity), deteriorating gait, and sensory loss. Manual muscle testing, performed serially by trained physical therapists at least yearly, provides a *quantifiable and reliable assessment of motor function with interobserver reliability*. A consistent decrease of at least one grade in several muscles is significant. Muscles innervated by the “last intact root,” with ascending weakness, or patchy muscle weakness in multiple muscles innervated by more rostral spinal levels may develop. Spasticity, hyperreflexia and/or clonus, progressive muscle contractures, and/or deteriorating gait may be present. Gait deterioration from tethering is the result of progressive muscle weakness, increasing spasticity, or orthopedic deformities; a progressive “sagging” gait due to hamstring or iliopsoas contractures is a common presentation. Subjective sensory complaints are relatively common, although objective

sensory changes are usually accompanied by other signs of neurologic deterioration.

Patients who have urologic deterioration may present with incontinence between catheterizations, an increase in the frequency of catheterizations, or more frequent urinary tract infections without another cause. If found, bladder infections should be treated before the urologic changes are ascribed to tethering. Bladder function is objectively assessed with serial urodynamic testing.^{72,169} A progressively smaller bladder capacity and/or increased bladder pressures, reduced thresholds for initiating bladder contractions (uninhibited bladder contractions), and bladder contractions against a closed urethral sphincter (detrusor–sphincter dyssynergia) are all potential signs of tethering. Bladders with high intraluminal pressures (>40 cm H₂O) and those with uninhibited contractions or dyssynergia increase the risk to the upper urinary tract. Urologic improvement occurs in approximately 60% of patients after untethering.¹⁵² Less common abnormalities of defecation may also improve after untethering.¹⁵²

Orthopedic deformities are common and their etiology is multifactorial, but tethering may contribute to progressive orthopedic deformities, including hip subluxation, pes cavus, and equinovarus deformities. Associated weakness, bladder dysfunction, or pain may provide additional evidence. For those with only orthopedic deformities, untethering may be performed initially in the hope of reversing the orthopedic deformity, or the underlying orthopedic deformity may be corrected and untethering reserved for those with recurring deformities. No studies have directly compared the outcomes of these two approaches.

Finally, scoliosis occurs in up to 90% of children with MMC^{170, 171} and is more frequent among those with thoracic and upper lumbar lesions.¹⁵⁶ Scoliosis is multifactorial and the result of paravertebral muscle weakness and sensorimotor imbalance, vertebral malformations such as hemivertebrae and segmental bars, pelvic obliquity or hip contractures, and/or neurosurgical conditions (Chiari malformation, syringomyelia, and spinal cord tethering).^{156,170} The *frequency* of scoliosis increases with both higher-level lesions and *older* age, whereas the *progression* of scoliosis (once present) correlates with a higher degree of curvature, *younger* age, and nonambulatory status. Scoliosis may be stabilized or reversed with untethering, particularly in those with midlumbar-level lesions and initial curves of less than 45 degrees; low-lumbar and sacral lesions are also likely to benefit, although the low incidence of scoliosis in this group precludes a meaningful analysis. In contrast, there appears to be little benefit to untethering for high-lumbar and thoracic lesions and for those with curves of more than 45 to 55 degrees. Although there is a fear that corrective scoliosis surgery without a prior “prophylactic” untethering will result in neurologic worsening from tethering or the Chiari malformation, there is no evidence to support this.¹⁷² Among 17 patients who underwent scoliosis correction (average improvement of 47 degrees) without prior untethering, none had neurologic deterioration or shunt malfunction.¹⁷³

Once again, the evaluation of tethering always begins with an assessment of shunt function. A malfunctioning shunt should be revised and the child reassessed several weeks postoperatively; if there is no clinical improvement, tethering is then considered. Adjuncts to evaluation include manual muscle testing,

urodynamic studies, and/or scoliosis radiographs. MR imaging of the entire spinal cord confirms tethering radiographically; identifies associated lesions such as lipomas, split-cord malformations, hydromyelia, and spinal stenosis, which may contribute to neurologic deterioration; and provides important surgical landmarks. However, *radiographic* signs of tethering alone do not determine the need for surgery in the absence of *clinical* deterioration.

Untethering involves reopening the previous closure and extending it slightly cranially to identify the last formed spinal segment (which can be removed if necessary to expose normal dura). The exposed dura is opened in a cranial to caudal direction; the surgeon works from normal spinal cord toward the placode and dissects the scarred placode and nerve roots from the dura. If possible, dissecting between the dura and arachnoid minimizes injury to the dorsolaterally adherent nerve roots. Other tethering lesions (lipomas, filum terminale, midline bands from split-cord malformations) are also untethered. Occasionally, the placode is so scarred that complete untethering is impossible; the goal is to untether as much as is safely possible. For children with no functional leg movements, some surgeons amputate the placode (the ultimate untethering). However, urologic deterioration occurs in 8%,^{95,96} and we therefore do not recommend this. Once untethering is complete, a primary dural closure is usually adequate; dural grafts are rarely necessary and do not appear to decrease retethering rates.

Complications are uncommon; neurologic or urologic worsening occurs in 3 to 5%. Postoperative symptomatic pseudomeningoceles or CSF leaks are infrequent and if present should suggest an occult shunt malfunction. Long-term outcomes are good.¹⁶⁸ In one study, pain improved in nearly 100%; weakness improved in 70%, stabilized in 28%, and deteriorated in 2%; spasticity improved in 63% and stabilized in 37%; gait improved in 79%, stabilized in 19%, and worsened in 3%; and bladder function improved in 67%, stabilized in 30%, and deteriorated in 3%. A second untethering was required in about 30% of those undergoing a tethered cord release. Of those requiring a second untethering, 39% required a third, and of these, 13% required a fourth release.¹⁶⁸ Although the mechanism is unclear, signs and symptoms characteristically ascribed to the Chiari 2 malformation may also improve after untethering, including nystagmus (66%), headache (69%), and upper extremity sensory loss (100%), although none resolved completely.¹⁷⁴

Management of Hydrosyringomyelia

Hydrosyringomyelia is present in 50 to 80% of patients with MMC^{67,175,176} but is symptomatic in only about 1.8 to 5%.¹⁷⁷ Again, *clinical deterioration* directs management, and clinical judgment is critical in selecting patients for treatment because

symptoms and signs may overlap those from spinal cord tethering and Chiari malformation. Clinical features may include upper extremity weakness, loss of function, and/or deformities (claw hand); neck or back pain; scoliosis; ascending motor loss; or increasing leg spasticity. The classic cape distribution “dissociated sensory loss” (loss of pain and/or thermal sensation with preserved light touch and proprioception)¹⁷⁸ is uncommon in our experience. Brainstem extension (syringobulbia) may produce brainstem dysfunction. Changes in urinary function are rare and should suggest spinal cord tethering.¹⁷⁸ Scoliosis due to hydrosyringomyelia is often rapidly progressive and thought to result from asymmetric anterior motor column damage.^{179–181}

Small or moderate-size hydrosyringomyelia cavities that are asymptomatic do not require treatment because the risks outweigh the benefits. Symptomatic hydrosyringomyelia may also reflect an underlying shunt malfunction.^{179,182} Treatment for symptomatic hydrosyringomyelia is controversial. Surgical options include Chiari decompression, syringo-subarachnoid stent, syringoperitoneal or syringopleural shunt, myelotomy, and tethered cord release.¹⁷⁷ Unfortunately, the literature is limited to case reports and retrospective series with only short-term radiologic or clinical success in some patients following all of the various treatments. Sklar and Shapiro analyzed outcomes of various treatments in 50 patients with MMC and hydrosyringomyelia. Posterior fossa decompression was successful (syrinx unchanged or decreased) in only 14% of patients, whereas syringo-subarachnoid stenting was successful in 70%. A combination of the two was successful in both children in whom it was performed. No syringoperitoneal or syringopleural shunts were performed in this series.¹⁸³

La Marca et al proposed a management algorithm (► Fig. 24.7) that divided hydrosyringomyelia into segmental (involving only a segment of spinal cord) and holocord (involving the entire spinal cord) types. Each type was further subdivided into mild, moderate, and severe forms; treatment in this series was reserved for those with moderate or severe forms. Finally, they described three groups based on clinical presentation: group 1, with predominantly Chiari-like symptoms (neck pain, stridor or vocal paresis, swallowing difficulties, or arm symptoms); group 2, with predominantly tethering-like symptoms (back pain, scoliosis, sensorimotor changes in the legs, or bowel and bladder changes); and group 3, with mixed symptoms. Treatment was determined by both the anatomical type and the presenting clinical symptom complex: group 1 patients with either a holocord or segmental syrinx underwent Chiari decompression, whereas group 2 patients with either a holocord or segmental syrinx and group 3 patients with a segmental syrinx underwent an untethering procedure. Only group 3 patients with a holocord syrinx underwent a syrinx shunt. When

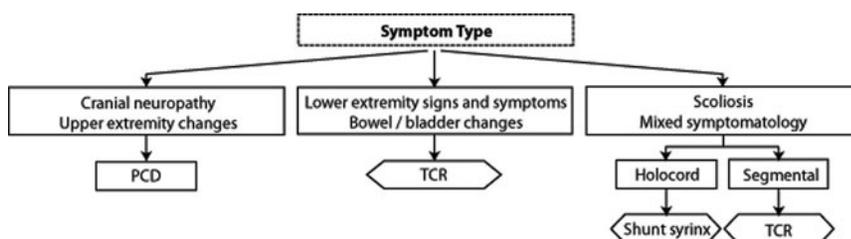


Fig. 24.7 Algorithm of LaMarca et al for treating symptomatic syringomyelia in children with myelomeningocele. PCD, TCR.

this algorithm was applied retrospectively to 45 patients, it led to better clinical and radiologic outcomes and fewer complications than were seen in those for whom the algorithm had not been followed.¹⁸⁴ Piatt, in a critical review of the existing literature,¹⁷⁷ concluded that the lack of class 1 or class 2 data precludes any firm treatment recommendations and suggested a multi-institutional cohort study using an algorithmic approach such as that proposed by La Marca et al.

24.4 Summary

The single greatest long-term neurosurgical problem for children with MMC remains the maintenance of proper shunt function. Every year, several children die as a result of unrecognized shunt malfunction; many of these deaths could be prevented if shunt malfunction were promptly recognized and dealt with. Understanding that the signs and symptoms of shunt malfunction in this population are legion and may not be associated with a change in ventricular size on CT scans will advance the care of these children considerably.

We reject the concept that delayed deterioration is simply the “natural history” of MMC; the cause of neurologic decline is eminently treatable in many cases. Aggressive treatment of associated neurosurgical disorders such as the Chiari malformation, hydrosyringomyelia, and spinal cord tethering has resulted in improved ambulation, better urinary function, and fewer orthopedic deformities; it has also obviated, in many cases, the need for spinal fusion and soft tissue releases for scoliosis and lower limb spasticity, respectively. With further advances, the outlook for these children remains ever more hopeful.

Pearls

1. Deterioration is not the natural history of MMC and has a potentially treatable cause. Any work-up for clinical deterioration should begin with a consideration of shunt malfunction.
2. Shunt malfunction may occur without a change in ventricular size. Imaging that shows normal ventricular size, or no change in size compared with baseline, may not be sufficient to exclude a shunt malfunction, particularly if any signs or symptoms (headaches, emesis, seizures, deterioration in cognitive function or personality) suggest a shunt malfunction as the root cause for the deterioration.
3. Mild or moderate stable swallowing issues are common in early childhood and often improve over time as the child ages. Chiari decompression should be reserved for those having significant swallowing issues (tracheal aspiration, emesis with inability to maintain weight) or associated vocal cord weakness, stridor, or apnea, and it should be undertaken with extreme caution. Beyond infancy, Chiari symptoms are almost always due to occult shunt malfunction.
4. Once shunt malfunction has been excluded, neurologic deterioration is most commonly due to spinal cord tethering, and a tethered cord release is the best treatment option. Syringomyelia is common in children with MMC but is rarely symptomatic.

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25 Occult Spinal Dysraphism

D. D. Cochrane

The term *occult spinal dysraphism*¹ (OSD) refers to a group of disorders arising as a result of the malformation of midline dorsal neural, mesenchymal, and cutaneous ectodermal structures during embryogenesis. OSD was originally grouped by von Recklinghausen² with spina bifida aperta because they share defective lamination of the posterior arches and present as abnormalities of skin, fat, laminae, and neural tissue. Over the past two centuries, OSD has come to encompass diastematomyelia and split-cord malformation (SCM), meningocele manqué, dermal tract or sinus with and without intraspinal tumors, lipoma of the conus and/or filum, and other abnormalities of the filum.^{3,4}

Although these conditions vary in their clinical features, embryopathology, and response to treatment, the clinical disorders that are categorized as OSD have four features in common: (1) The major causes of neurologic impairment in these patients are spinal cord tethering, neural compression, and myelodysplasia; (2) when no surgical treatment is instituted, patients may develop progressive neurologic deficits as a result of cord tethering, trauma, or compression; (3) progressive and evolving deficits are amenable to surgical intervention, whereas static deficits are not⁵⁻⁸; and (4) anatomical and postoperative clinical retethering occurs and requires that these patients be monitored for neurologic, urologic, and orthopedic deterioration, even after a successful operation.^{5,9}

The clinical features that characterize OSD have been the subject of interest through the ages. The “faun’s tail” that commonly accompanies diastematomyelia, the pes cavus, and the calf atrophy may have been the genesis of the satyr of Greek mythology.² Descriptions of SCMs, including the introduction of the term *diastematomyelia* with and without bony septum and fibrous bands, “all associated with greater or lesser degrees of spina bifida,” appeared in the late 19th century.¹⁰ The surgical significance of SCM had to await the reports of Marr and Uihlien 1944,¹¹ and of Matson et al in 1950.¹² The importance of congenital lipomas of the conus and filum was initially brought to attention by Bassett in 1950 in a report of patients who had lipomas of the conus and filum, presented with urinary incontinence due to neurogenic bladder, and recovered continence postoperatively. Walker and Bucy¹³ were the first to recognize the association between congenital dermal sinus, meningitis, and paralysis. Tethering of the spinal cord by the filum terminale as a cause of neurologic deterioration was a concept suspected by Garceau.¹⁴ Hoffman et al¹⁵ introduced the term *tethered cord syndrome* to refer to this entity. Subsequently, its use was expanded to include restricted cord movement with any and all etiologies.¹⁶

25.1 Epidemiology

The incidence of OSD in the general population is not known. Unlike the diagnosis of open defects, which are clinically obvious, that of closed defects requires awareness of the significance of cutaneous markers and often subtle neurologic deficits and musculoskeletal deformity. There is little information

regarding the risk factors predisposing to nonsyndromic closed spinal dysraphic states. The observation that open and closed neural tube defects may be genetically related¹⁷ suggests that at least some risk factors may apply to both types of spinal malformations. Studying 364 siblings of 207 patients with all forms of OSD, Carter et al found a 4% incidence of myelomeningocele or anencephaly in the series. Patients with OSD and families with caudal regression syndrome may share risk factors, in particular, maternal diabetes.^{18,19}

The incidence of anomalies associated with cord tethering, including imperforate anus, have been shown to decrease with the periconceptual consumption of folic acid.²⁰ However, dietary folic acid supplementation has not been shown to decrease the incidence of lipomyelomeningocele in Nova Scotia.²¹

25.2 Pathology and Pathogenesis

25.2.1 Intradural Lesions

Tight Filum Terminale

An abnormally tight filum terminale causes caudal traction on the spinal cord.^{4,14,15} The diagnosis is suspected on clinical grounds and confirmed when the conus position is abnormally low, or is in a normal position (above L2),^{15,22,23} by the presence of fat in the filum (“fatty filum” or “filum lipoma”)^{24,25} and/or a filum diameter greater than 2 mm (“thick filum”) (► Fig. 25.1). Although such findings (low conus, fatty filum, and thick filum) may be seen occasionally in isolation in a normal patient, the combination of two or more factors, coupled with the patient’s clinical status and/or the presence of bony dysraphism, should significantly increase the likelihood of finding a symptomatic tethered spinal cord.²⁶

Split-Cord Malformation (Diastematomyelia)

SCMs can be divided into two main types, classically termed *diastematomyelia*¹⁰ and *diplomylelia*, and were previously thought to have different embryologic origins. In an effort to provide a classification scheme with more consistent and clinically relevant terminology, Pang,^{27,28} building on the theories of Bremer²⁹ and the classification used by James and Lassman,⁴ suggested the use of SCM type 1 and SCM type 2. Type 1 SCM consists of two hemicords separated by an osteocartilaginous median septum, each housed in a separate dural sheath (► Fig. 25.2a). Type 2 SCM consists of two hemicords contained within the same dural envelope and separated by a fibrous septum (► Fig. 25.2b). Both SCM types are thought to be caused by an abnormal, persistent neurenteric canal between the yolk sac and amnion. This fistula later splits the neural canal and notochord by forming an endomesenchymal tract. The persistence of parts of the tract, the entrapment of different structures within it, or both, explain the subsequent development of associated malformations. Endodermal remnants predispose to the formation of neurenteric cysts and intestinal duplication, the lack of skin closure dorsal to the tract causes a dermal sinus

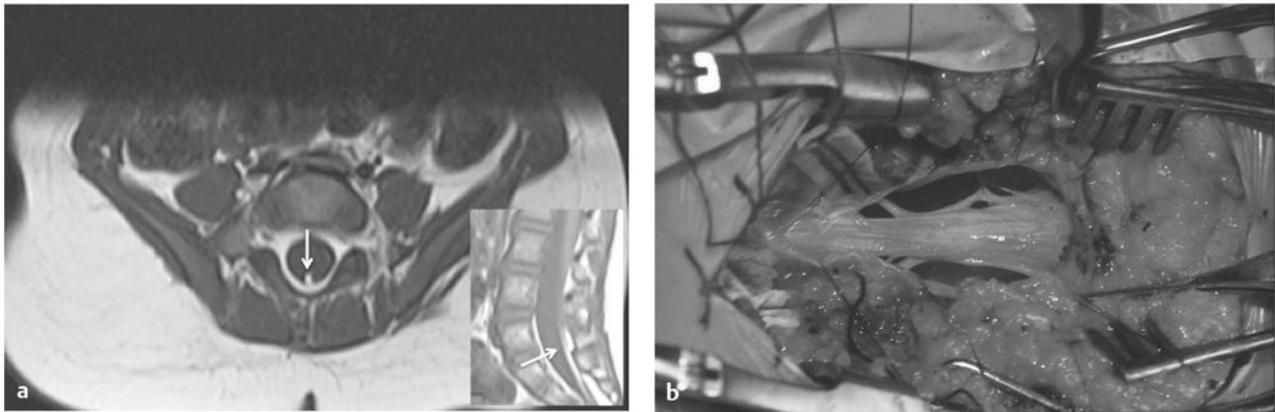


Fig. 25.1 (a) Transverse and midsagittal magnetic resonance images of a small infant with a tethered spinal cord resulting from a tight filum terminale. The conus is abnormally low (below L3), and the filum is enlarged and infiltrated with fat (arrows). (b) Thick, tethering filum terminale. Roots ascend to reach their exit foramina.

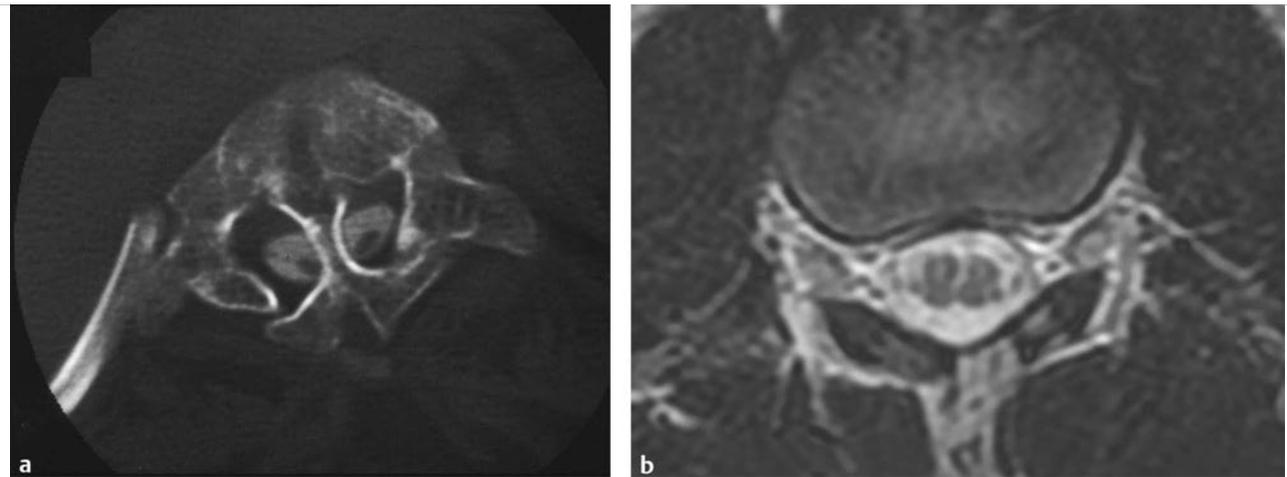


Fig. 25.2 (a) Computed tomographic myelogram of the upper lumbar spine. Dysmorphic bone is applied over the dorsal surface of the cord. A bony septum with a dural sleeve penetrates the split on this and adjacent images. (b) Axial magnetic resonance image of a type 2 split-cord malformation. The patient's symptoms were caused by tethering bands arising from the medial aspect of each hemicord and fixing the cord dorsally. The bands are not visualized on this study.

tract that may form a dermoid cyst, and the entrapment of neural crest elements within the endomesenchymal tract allows the formation of paramedian nerve roots and meningocele manqué.²⁸ A persistent endomesenchymal tract interfering with normal neurulation of the adjacent neural tube may explain the known association of SCM with open myelomeningocele.

Most if not all patients have *tethering* median septa, the residual of the neurenteric canal, that are not always visible on preoperative imaging studies. All lumbar SCMs have a low-lying conus and may have additional tethering lesions.²⁷

Meningocele Manqué (Dorsal Bands)

Meningocele manqué (dorsal bands) is an occult spinal lesion that, as the term implies, is a meningocele that failed to develop (from the French *manqué*, “missed” or “failed”) (► Fig. 25.3). According to James and Lassman,⁴ who coined the term, an open

meningocele “protrudes on the surface of the back and does not contain neural elements. But often, there are nerves that are adherent to the neck of the meningocele.” It is thought that a meningocele manqué is a meningocele that formed in the embryo, then underwent spontaneous healing or scarring. It is often described as a dorsal band with or without adherent nerve roots or dorsal root ganglia. These bands start in the intrathecal structures and extend up into the dura or lamina, thus possibly tethering the spinal cord. Histologically, these bands are composed of fibrous tissue that often contains meningeal elements. Most of these lesions are associated with other intradural lesions.^{30–33}

Dermal Sinus and Associated Tumors of Disordered Embryogenesis

Dermal sinus ► Fig. 25.4) and tumors of disordered embryogenesis result from incomplete separation of the neural ectoderm

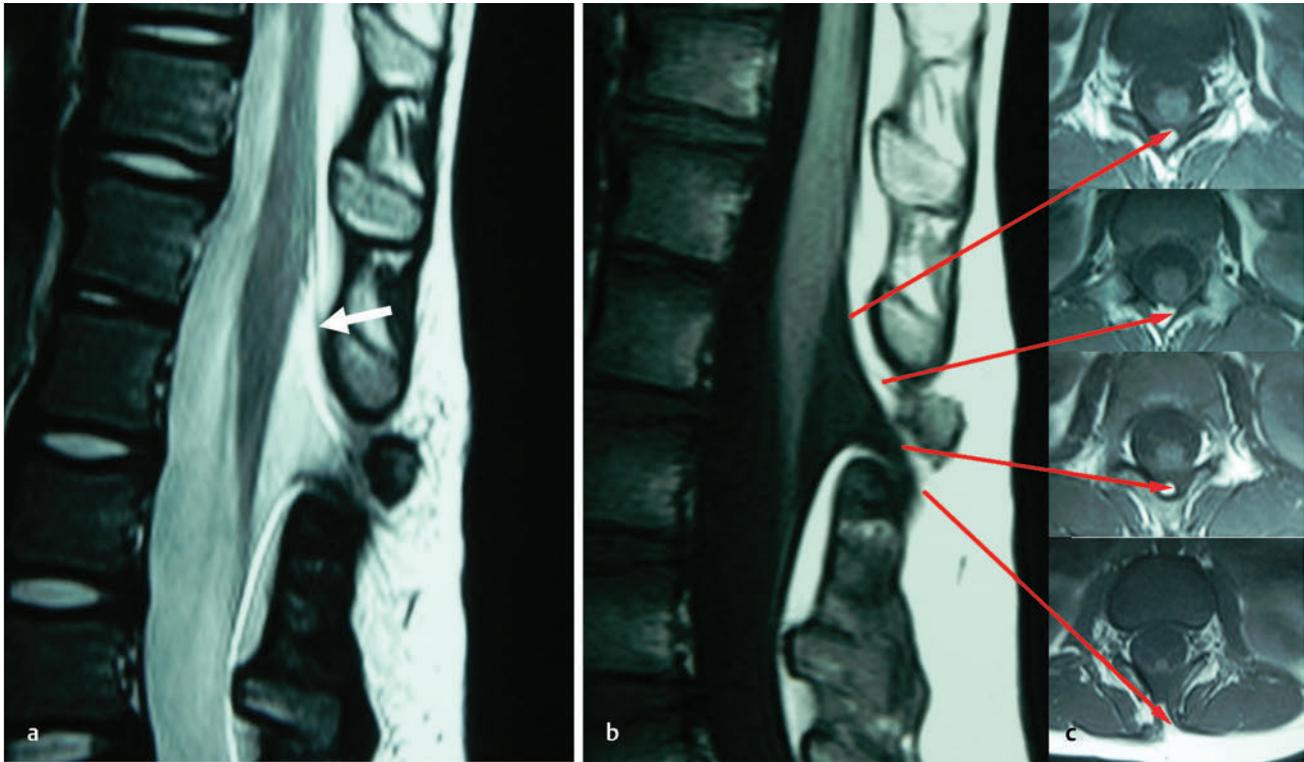


Fig. 25.3 (a) T2-weighted sagittal magnetic resonance (MR) image showing features of meningocele manqué, including a meningocele, tapered conus, dorsal tethering bands (*arrow*), and a rudimentary disk at level of the dysplastic lamina. (b) T1-weighted MR image of the same section as in (c) axial images. Adjacent axial images show a dorsal lipomatous stalk descending from the conus to exit the spinal canal through a bifid spinous process and passing into the subcutaneous fat (lowest image).

from the epithelial ectoderm (incomplete disjunction).³⁴ Dermal sinuses occur most commonly in the midline at the lumbosacral junction but are known to occur anywhere in the midline from the sacrum to the nasion and in rare situations may be off midline over either the spine or cranium. The sinus is lined with epithelium encased with dermis and fibroglial tissues. There may be hair protruding from the orifice of the sinus, itself often surrounded by avascular nevus. Most sinuses pass into the intradural space to end on the filum terminale or the conus. It is rare that they end in the subcutaneous tissues or extradural space.³⁵

Tumors may occur either independently or in association with a dermal sinus tract. Dermoid tumors occur in 80% of patients and contain elements from two germ layers (e.g., skin, hair, sweat, and sebaceous glands). Epidermoid tumors (20%) contain only desquamated cells from the epidermal layer. Intradural teratomas, which are more unusual, contain elements from all three germ layers. Malignancy is rare. Dermoid tumors may present as a midline subcutaneous mass, may be embedded in the central canal of the spinal cord, or may appear anywhere between these two extremes. The wall of the cyst contains the epithelial elements that are associated with regrowth of the cyst; thus, the focus of the resection must be to remove all epithelial remnants if possible.^{4,34}

Terminal Syrinx

A terminal syrinx (► Fig. 25.5^{30,36}) is a cystic dilatation of the lower third of the spinal cord. It generally occurs cephalad to

other OSD defects (tight filum terminale associated with an anorectal anomaly, meningocele manqué, diastematomyelia, and lipoma of the conus) and less frequently with other spinal cord anomalies.³⁰ It is present in about one-third of cases of OSD evaluated by magnetic resonance (MR) imaging, and two-thirds of these are large and likely to cause pain, motor weakness, and bowel and bladder deficits. Terminal syrinx should be suspected as a cause of delayed deterioration in function in a patient with OSD.

A myelocystocele (► Fig. 25.6) is probably a severe form of terminal syrinx that balloons out to form a large terminal cyst that tethers the spinal cord. The cyst sits in a large cavity that consists of an arachnoid-lined meningocele.^{37–39} This meningocele is in continuity with the subarachnoid space and is associated with dorsal bony dysraphism. The myelocystocele may be continuous with a syrinx and may be associated with a lipomatous mass, hence the terms *lipomyelocystocele* and *cystolipomyelomeningocele*.⁴⁰ For unknown reasons, myelocystoceles have been strongly associated with the teratogenic agent retinoic acid, as well as with the OEIS (*omphalocele, cloacal extrophy, imperforate anus, spinal anomalies*) syndrome.^{41,42}

25.3 Pathophysiology

Intradural dysraphic lesions cause neurologic deficits in several interrelated ways: (1) They may be due to abnormal formation of the neural structures during intrauterine development; (2)

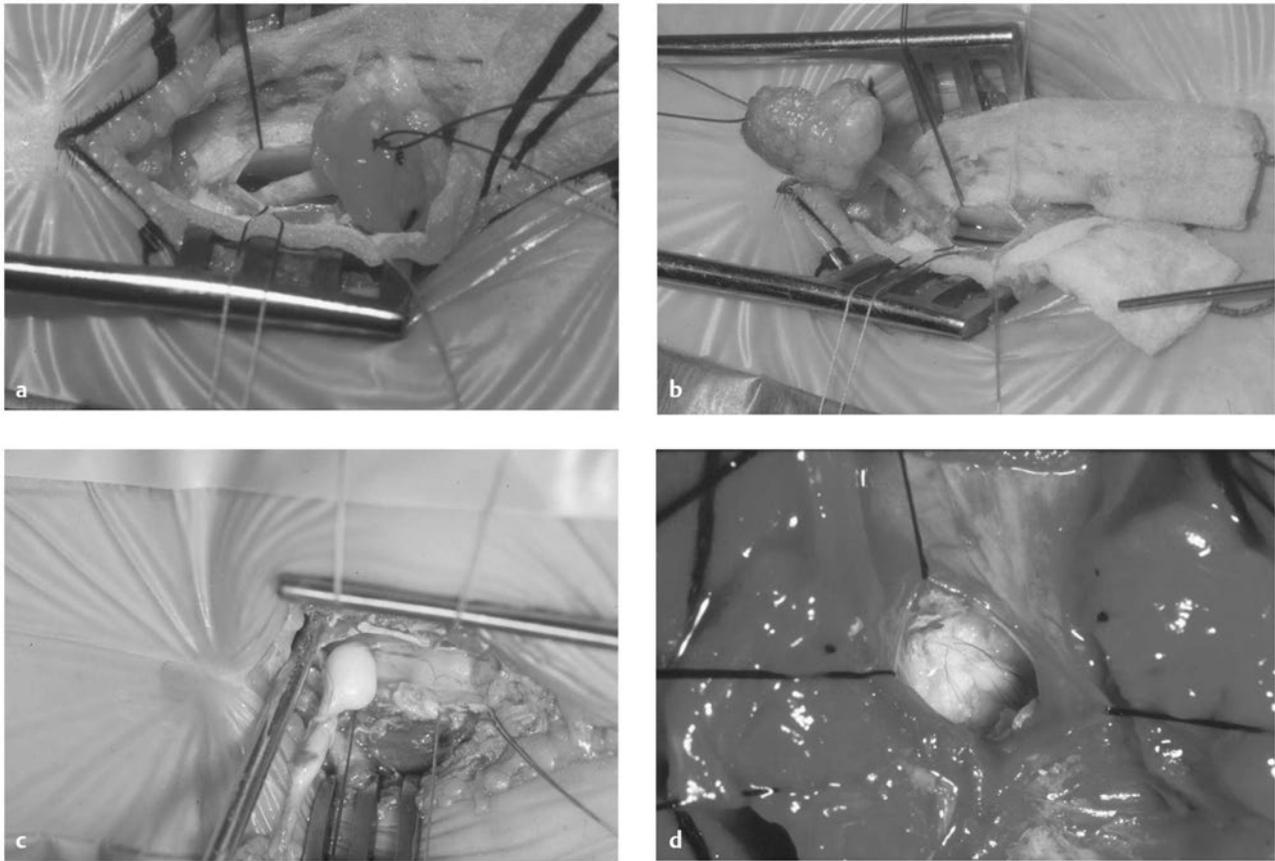


Fig. 25.4 (a) Dermal sinus and tract passing through dura to attach to the dorsal surface of the conus. (b) Dermal sinus tract is easily separated from the cauda equina and filum. (c) Dermoid tumor in the dermal sinus tract. (d) Dermoid tumor containing desquamated epithelium and hair.

lesions such as a lipoma of the conus or tumors of disordered embryogenesis may compress or expand within the conus medullaris; and (3) these lesions may cause traction on the radicular and medullary vasculature, spinal cord, and nerve roots by tethering these structures to surrounding spinal canal, dura, or extradural tissues. Such tethering is thought to interfere with normal, growth-related cord, root, and vascular motion, resulting in excessive tension within the cord.^{16,43,44} Tethering may cause traction on the conus medullaris or cord caudally (e.g., tight filum terminale and lipomyelomeningocele); dorsally (e.g., meningocele manqué, dorsal band, and dermal sinus tract); ventrally (e.g., ventral band, diastematomyelia, and neurenteric cyst); or in several directions simultaneously (varieties of complex lipoma of the conus). In addition, neurologic impairment may be due to meningitis or abscess complicating a dermal sinus or to hemorrhage into a neurenteric cyst.

Tethering is thought to be a major contributor to the deterioration in function noted over time in patients with OSD.^{16,45-47} Experimental evidence has shown that traction causes ischemic changes to the spinal cord.^{16,43-46} Repetitive flexion and extension of the spine and other sudden violent movements of the body are thought to cause ischemia to the tethered spinal cord as well as direct trauma at the point of fixation.^{16,48,49} Repetitive motion of the cord and roots, driven

by cerebral spinal fluid (CSF) pressure and flow changes, is also likely to be contributory to cord injury.⁵⁰ Similarly, spinal cord traction is thought to worsen with growth of the spinal column during childhood, thus explaining the progression of the neurologic deficit over time. Traction on the spinal cord is seen to cause maximal cord elongation in the lumbar region, with less physical damage or “stretchability” in the thoracic and cervical areas.^{16,48} This finding fits the usual clinical scenario of maximum lumbosacral cord dysfunction with the tethered cord syndrome. MR imaging of cord motion has confirmed that cord motion is decreased in patients with tethering and has suggested that the prognosis for neurologic recovery is worse in patients who had markedly decreased cord motion preoperatively.⁵¹⁻⁵³

25.4 Presentation

25.4.1 Signs and Symptoms

Patients with occult spinal dysraphism (OSD) may present with a combination of cutaneous, orthopedic, urologic, and neurologic signs and symptoms. The box “Signs and Symptoms of OSD” (p.312) lists the patterns of clinical presentation and manifestations that suggest the diagnosis of OSD.^{4,54} As the knowledge of OSD broadens among practitioners, many cases will be

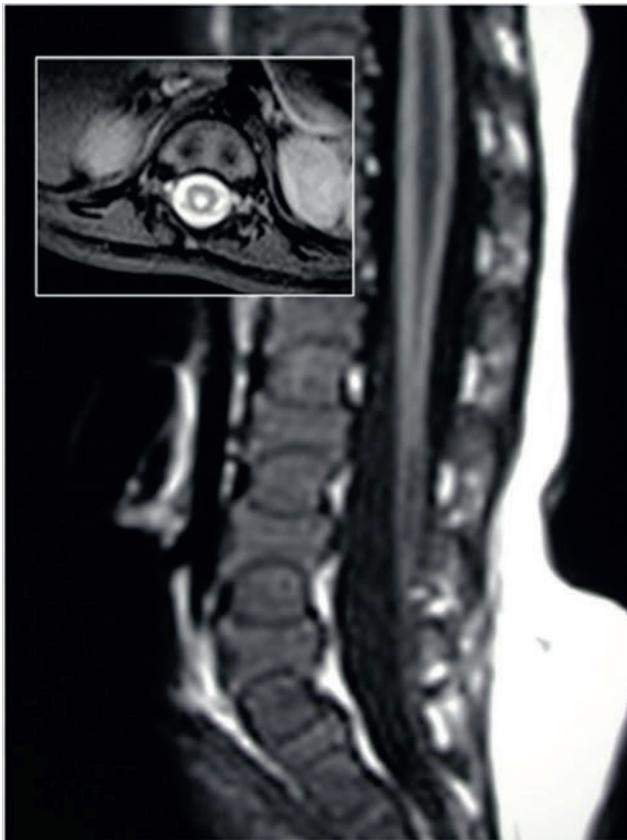


Fig. 25.5 Magnetic resonance image of the lumbar spine of an infant with a moderate-size syrinx and a conus tethered by a thickened filum. Insert shows the extent of the syrinx in the transverse plane.

recognized in infancy and childhood based on the clinical syndrome of cutaneous anomaly, subtle or progressive neurologic deficits including urinary incontinence, and musculoskeletal asymmetry.

Patterns of Clinical Presentation

- Asymptomatic infant with cutaneous marker
- Asymptomatic infant or child with caudal regression syndrome
- Symptomatic child with incontinence/evolving neurologic or orthopedic anomalies.
- Symptomatic child with secondary incontinence and a normal filum on MR imaging (occult tethered cord syndrome).

25.4.2 Clinical Context

The clinical context in which the patient presents can be the same for a number of pathologic forms of OSD. Although certain cutaneous markers and skeletal deformities are relatively specific for underlying spinal cord abnormalities (see box “Signs and Symptoms of OSD” (p.312)), many are not and are defined only after spinal MR imaging or ultrasound. In general, the clinical presentation falls into one of the following categories:

- Asymptomatic infant with cutaneous marker
- Asymptomatic infant or child with caudal regression syndrome

- Symptomatic child with incontinence/evolving neurologic or orthopedic anomalies
- Symptomatic child with secondary incontinence and a normal filum on MR imaging (occult tethered cord syndrome)

Signs and Symptoms of OSD

- Cutaneous stigmata
- Hypertrichosis
- Orthopedic deformities
- Foot and leg deformities and asymmetry
- Scoliosis
- Urologic problems
- Neurogenic bladder
- Urinary tract infections
- Incontinence
- Neurologic symptoms and signs

– Infants
Decreased spontaneous leg movement

Absent reflexes

Leg atrophy hidden by baby fat

Foot asymmetry

– Toddlers

Development delay (walking)

Abnormal gait

– Older children

Asymmetric motor and sensory dysfunction

Painless foot burns

Upper motor neuron signs (hyperreflexia)

Back and leg pain

– Young adults

Back and leg pain, either chronically or acutely after trauma or hyperflexion

Spasticity and hyperreflexia

– Any age

Meningitis

Paraplegia

Asymptomatic Infant with Cutaneous Marker

The incidence of significant cutaneous lesions of the craniospinal axis in the general population of neonates was found to be 3% in a large prospective study,⁵⁵ whereas in patients with OSD, the incidence approaches 80%,^{4,7} and it is common for two or more cutaneous lesions to coexist.⁵⁶ Cutaneous anomalies occur in the midline of the back, are above the level of the coccyx, and commonly overlie the spinal lesion. In general, the complexity of the cutaneous lesion reflects the degree of developmental anomaly of the underlying neural structures (see box “Signs and Symptoms of OSD” (p.312)). The cutaneous lesions associated with abnormalities of the filum, tethering bands, tracts, and neurenteric cysts include dimple, subcutaneous lipoma, dermal appendages, deviated or forked intergluteal cleft, vascular nevus, and/or pigmented nevus.⁵⁷

In *hypertrichosis*, tufts of hair may be sparse but more commonly are profuse, earning the name “faun’s tail” or “horse’s tail” (► Fig. 25.7a,b).^{2,4} There is a strong association between hair tufts and SCM, especially the form with a median bony septum (type 1). In the series of James and Lassman, hypertri-

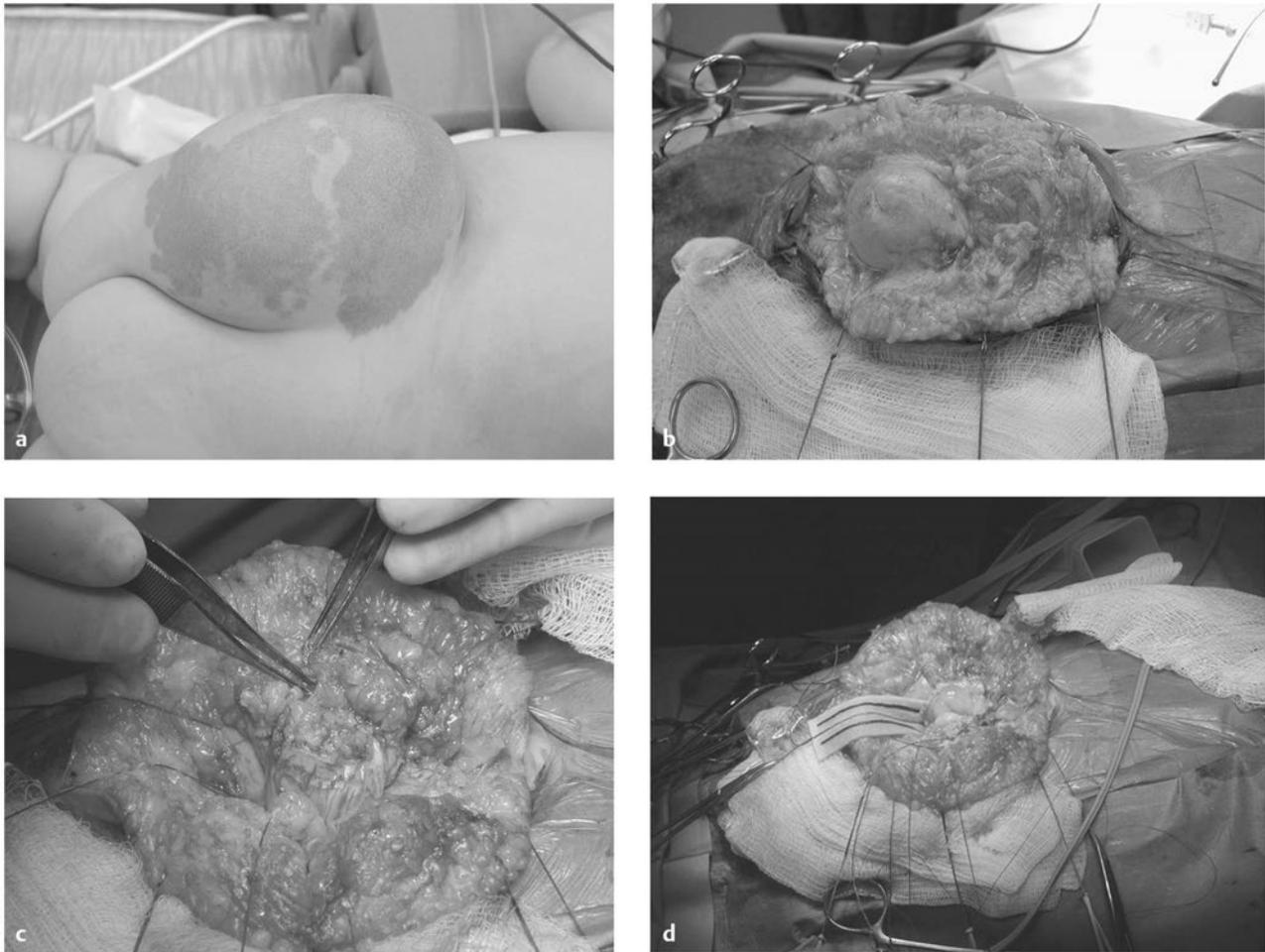


Fig. 25.6 (a) Lipomyelocystocele. Spinal ultrasound demonstrated several cerebrospinal fluid (CSF)-containing spaces. The terminal myelocystocele was recognized with gentle ballottement of the mass and observation of expansion of the central canal rostral to the lesion. The other CSF space was presumed to be a meningocele. (b) Exposure of the meningocele. (c) Meningocele opened. Lateral aspect of the myelocystocele at the lipoma-root interface clearly seen. (d) Meningocele and myelocystocele opened. Central canal in view.

chosis, especially the profuse form, occurred in 67% of cases of diastematomyelia with a median septum and in 33% of cases without a septum. In the same series, hypertrichosis also occurred in 24% of patients with spinal anomalies other than diastematomyelia.⁴

Atretic meningocele is a midline area that represents a meningocele that was present in fetal life and has subsequently atrophied or partially healed (► Fig. 25.7c,d). The skin can be quite thin, with the bluish hue of CSF underneath. Bands may connect the base of the skin defect to the dorsal surface of the spinal cord, and the lesion can be quite sensitive to touch, even in neonates. *Aplasia cutis* is often a small midline circular defect, in the past likened to a cigarette burn that commonly overlies a tethering dermal or fibrous tract. Atretic meningocele can be differentiated from aplasia cutis by the absence of the bluish hue in aplasia and the presence of a tract on imaging.

A *dermal sinus* is an opening in the skin that may connect to a subcutaneous tract lined by epithelium that can be traced to the dura or spinal cord (► Fig. 25.8). The orifice is commonly raised, with one or more stiff hairs sprouting, and it may have

at its base a cutaneous hemangioma or nevus. Intradurally, it may be associated with any of the other major dysraphic anomalies, and half of the tracts that enter the spinal canal end in a dermoid or other inclusion cyst or tumor.³⁴ A dermal sinus is especially significant among the cutaneous stigmata of OSD because in addition to its role as a sign of intradural pathology, it provides access for bacterial contamination that can result in local infection, meningitis, and/or intramedullary abscess.⁵⁸ Such infections do not always have cutaneous manifestations (i.e., redness, swelling around the sinus opening). A dermal sinus should be distinguished from the common sacrococcygeal or dermal pit. The latter is always located in the intergluteal fold directly over the tip of the coccyx. Coccygeal dermal pits are not associated with OSD, and when seen in isolation, they require neither surgery nor radiographic evaluation.⁵⁹

Dermal appendages can take many forms, some complex and reminiscent of abortive twinning^{60,61} (► Fig. 25.9). More commonly, they are simple, skin-covered mesenchyme-containing structures that resemble a tail. A *pseudotail* is any cylindrical outgrowth from the lumbosacral area (► Fig. 25.10); it is usually



Fig. 25.7 (a,b) Faun's tail. Luxuriant hair reminiscent of the tail of a satyr. (c) Infant with focal hirsutism superimposed on a background of flat capillary hemangioma. The central aspect of the lesion is composed of thin, atrophic skin and is exquisitely sensitive to touch. From the base of the lesion, strands of tissue extended to the dorsal surface of the spinal cord, which they tethered. (d) Aplasia cutis. The cigarette burn of old. This may mark a dermal tract without sinus, or meningocele manqué.

short and stumplike and may contain fat, cartilage, or other organ-specific tissue, such as embryonic kidney.^{62,63} In contrast, a *true human tail* is a remnant of an embryonic structure containing vertebrae, notochord, and spinal cord, as well as a sacral artery and vein; it may contain muscle in addition to adipose and connective tissues and may be curved, pigmented, or covered by hair; it is often “capable of spontaneous or reflex motion.”⁶²

An asymmetric or forked gluteal cleft is often associated with a capillary hemangioma or dermal appendage.

The presence of a capillary hemangioma, either flat or raised (strawberry), in the midline over the spine raises the suggestion of an underlying dysraphic defect,^{4,64} in particular when it is associated with other cutaneous anomalies (lipoma, dimple, asymmetric gluteal cleft). The incidence of underlying dysraphism is low with an isolated lumbosacral midline strawberry hemangioma⁶⁵ but is higher in the presence of a flat capillary hemangioma⁶⁶ (► Fig. 25.11). Like a capillary hemangioma, a pigmented nevus is rarely a marker of OSD when it occurs in

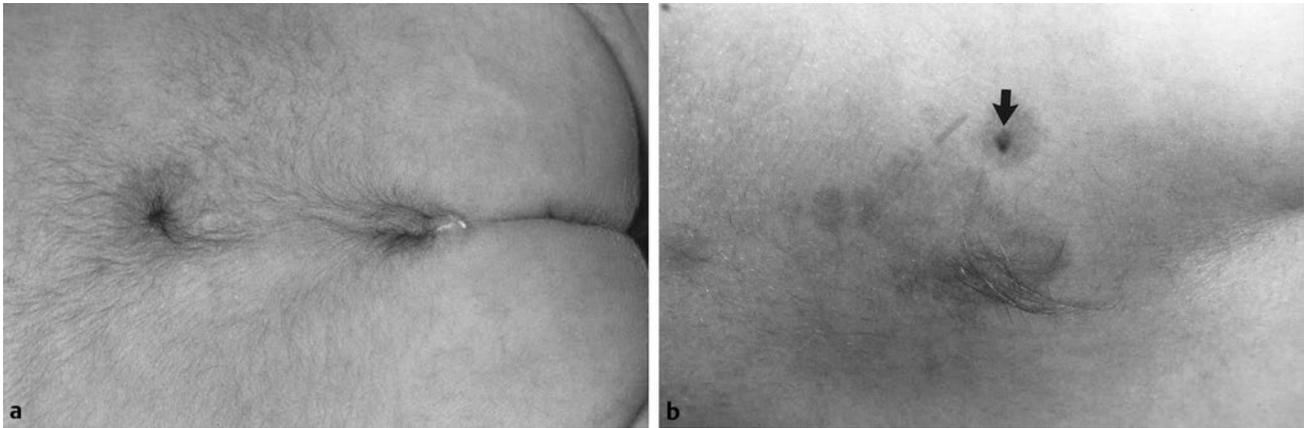


Fig. 25.8 (a) Dermal sinus—elevated orifice, stiff hair, and basal hemangioma. (b) Lumbar region of an infant with three cutaneous signatures of occult spinal dysraphism: dermal sinus (*arrow*), small area of focal hirsutism, and a flat capillary hemangioma under both of the other lesions. At operation, the dermal sinus was found to penetrate the dura and ascend to the conus; there was a short segment of diastematomyelia without a median septum, and the filum was enlarged and infiltrated with fat.

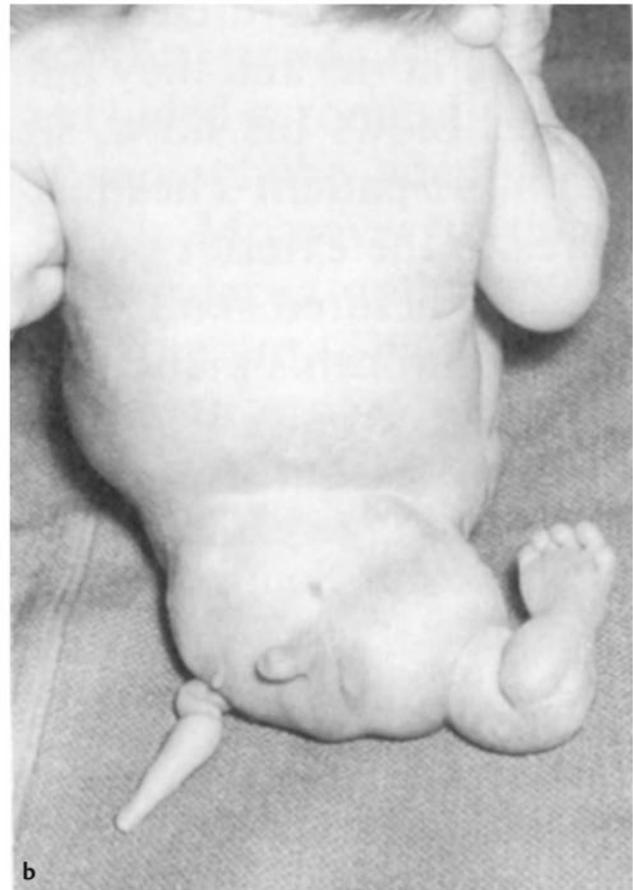


Fig. 25.9 (a–c) Examples of complex dermal and mesenchymal appendages. ([a] and [b] From Parkinson D. Accessory limbs and spinal dysraphism. *J Neurosurg* 1991;75:498–499.61 [c] From Humphreys R, Manwaring KH, Carroll N. Accessory arm—dysraphism of disparity. *J Neurosurg* 1991;74: 297–300.60 Reprinted with permission.)



Fig. 25.10 (a) Small midlumbar appendage is easily seen. It has a very narrow neck and was easily excised, leaving a small scar. Imaging was performed, and a tethered spinal cord was clearly noted. The cord was untethered prophylactically, and the patient remains neurologically intact. (b) Another appendage, this one associated with rectal stenosis. Again, this is a cutaneous signature of occult spinal dysraphism. (c) Dermal appendage marking a lipoma of the filum. (d) Dermal appendage associated with terminal lipoma of the conus.

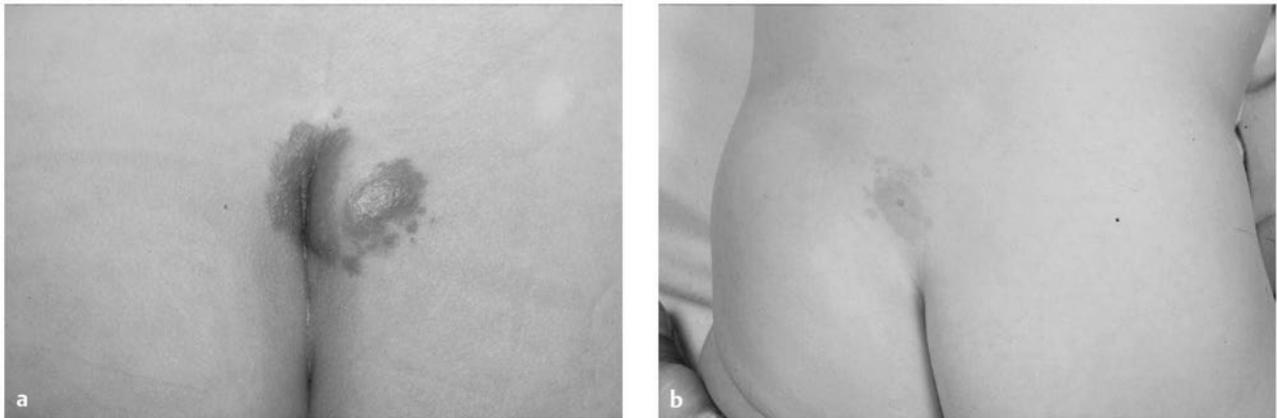


Fig. 25.11 (a) Intergluteal hemangioma marking lipoma of the filum. (b) Capillary hemangioma and dermal sinus.

isolation, and mongolian spots are not markers of underlying spinal dysraphism.

These skin lesions are present at birth and often lead to an ultrasound or MR examination to detect intraspinal anomalies. The detection rate for tethered cord abnormalities varies in

individual series, some reporting a high sensitivity and others low.⁵⁷ Given the concerns regarding general anesthesia⁶⁷ in this age group, it is the practice of this author to defer general anesthesia for MR evaluation in an asymptomatic infant until after 1 year of age if the ultrasound assessment is nondiagnostic.

Asymptomatic Infant or Child with Caudal Regression Syndrome

Caudal agenesis⁶⁸⁻⁷¹ comprises a spectrum of sporadic congenital malformations arising from the caudal embryo. The range of hindgut and urogenital malformations^{69,70} that occur secondary to caudal agenesis include stenotic or imperforate anus; rectovaginal or rectourethral fistula; persistent cloaca resulting in a common urinary, genital, and intestinal outflow structure; and cloacal exstrophy. The complex developmental anomalies shown to be associated with spinal cord tethering include the following: (1) OEIS syndrome⁴¹ (omphalocele, cloacal exstrophy, imperforate anus, and spinal anomalies); (2) VATER syndrome⁷² (vertebral anomalies, anal imperforation, tracheoesophageal fistula, and renal radial anomalies); (3) VACTERL association (vertebral defects, anal atresia, cardiovascular anomalies, tracheoesophageal fistulas, renal anomalies, and limb defects, most often of the radius); and (4) the Currarino triad (anorectal malformation, sacral anomalies, and presacral masses). The more complex the developmental anomaly, the more frequently OSD is found,⁷³⁻⁷⁷ with incidence rates ranging from 15% in patients with an isolated imperforate anus (high or low)⁷⁸ to 60% in those with the VACTERL association.⁷⁹ Filum lipoma, thickened filum, lipomyelomeningocele, ependymal cysts, and myelomeningocele have been reported as the common tethering pathologies in these entities.

The role of the tethered cord in the functional impairment that these patients exhibit is not usually clear because of the pelvic floor, sphincter, and muscular malformations that directly affect urinary and bowel continence. Cord untethering is indicated for patients showing neurologic or motor deterioration; however, prophylactic untethering in the hope of improving continence is not necessarily indicated.⁸⁰

Infants with caudal regression syndrome have typical clinical findings.⁷⁰ A narrow pelvis results from the absence of vertebral segments and is accompanied by flattening of the buttocks, shortening of the intergluteal cleft, and prominence of the iliac crests. The missing coccyx and sacral elements may be obvious on palpation of the spine. Disturbance of lower extremity motor function is often accompanied by the relative preservation of sensory function. Treatment of the gastrointestinal and urogenital anomalies takes priority because of the possibility of life-threatening complications if they are left untreated.²⁵

Symptomatic Child with Incontinence/ Evolving Neurologic or Orthopedic Anomalies

No characteristic neurologic symptoms or signs occur in a patient with closed spinal dysraphism. The presentations range from back or leg pain, to subtle bladder disturbances detected with urodynamics, to a mild sensory disturbance in one foot, to severe motor deficits and resultant leg atrophy and deformity. The neurologic deficits are typically asymmetric, regardless of the type or location of the spinal lesion.^{4,9} Before a child begins to walk, it is often difficult to detect muscular weakness. Often, the deficit is mild and evidenced only by a slight asymmetry of the feet (possibly indicating long-standing motor weakness) or a predisposition to painless foot ulcers. The difficulty with diagnosis is especially true in newborns, in whom a thorough neurologic examination is particularly challenging and in whom

lower extremity changes become more evident over time as a consequence of the effects of muscle imbalance, weight bearing, and gravity on developmentally malformed bone and joint structures.⁸¹ Even unilateral atrophy of the leg muscles in an infant may be hidden by the abundant subcutaneous fat, and decreased spontaneous movements or an unusual posture of one extremity or asymmetric use may be an indication of subtle motor weakness.⁴⁵ Delayed or asymmetric ambulation in an infant may be the initial complaint.

Rarely, infants with terminal myelocystocele may deteriorate quickly. The deterioration may be due to an increase in CSF volume within a terminal myelocystocele and syrinx⁸² and/or displacement of CSF into a terminal syrinx, with cord distention caused by supine positioning. Acute deterioration can also occur as a result of hyperflexion movement(s).

Unilateral or bilateral foot deformities⁴ are the most common deformities reflecting OSD and include club feet; valgus, varus, and cavovarus deformities; hallux varus; asymmetric toe size; and trophic foot ulceration. Anomalies may be subtle, especially in infancy, and may consist of an increase in the web space or a difference in the slope of the arch; these are best viewed by looking at the soles of both feet simultaneously. Buttock asymmetry with a lateral curve to the upper part of the gluteal crease is a subtle sign that can easily be overlooked. Spasticity, as well as analgesia-related trophic ulcers and fatigue fractures, may also be obvious in an older child.^{4,83,84} Because of underlying malformed bone and joints, a foot deformity may worsen after repair of a spinal anomaly.^{4,81}

Patients harboring a dermal sinus usually present because the cutaneous marker is recognized. However, if this is missed or its significance is not appreciated, meningitis, often due to *Staphylococcus aureus*, *Escherichia coli*, or *Proteus* species, is the most common mode of presentation.¹³ Infection of an associated intraspinal dermoid tumor can result in acute paraplegia from either conus or cauda equina compression. As with other intradural tumors, spinal pain is a prominent feature.

Depending upon age, scoliosis occurs in up to 25% of patients with a tight filum terminale and 90% of patients with SCM. Factors that increase the likelihood of an intraspinal anomaly included the following: (1) thoracic curve convex to the left (23% of patients with left thoracic scoliosis had an intraspinal anomaly, versus 8% of patients with other curve patterns); (2) age younger than 11 years; (3) severe scoliotic curvature (the major curve averaged 57 degrees for the group with intraspinal anomalies and 28 degrees for the others); and (4) rapid progression of the curve (average of 28 degrees per year).⁸⁵

Symptomatic Child with Secondary Incontinence and a Normal Filum on Magnetic Resonance Imaging (Occult Tethered Cord Syndrome)

Children who present with incontinence but no structural or functional urologic abnormality should be investigated for evidence of OSD, whether or not they have a cutaneous marker. The loss of urinary control may be primary when daytime and nighttime continence has never been acquired, or secondary when loss of control occurs after a period of normal daytime and nighttime continence. Several series have reported

improvement in incontinence following section of a structurally normal filum associated with a normally positioned conus.⁸⁶⁻⁸⁹ At the present time, the clinical and urodynamic characteristics that predict continence following filum section are not clearly defined, and opinion among experts differs as to the role of untethering.⁹⁰ It is hoped that a randomized clinical trial, currently in process, will provide clarity as to the operative indications in this clinical context. Until the results of this study are available, section of the normal filum for incontinence should be considered experimental.

25.5 Diagnostic Studies

25.5.1 Magnetic Resonance Imaging

Spinal MR imaging is the imaging procedure of choice to diagnose and follow patients with OSD. Its multiplanar imaging capability and the ability to visualize and differentiate neural tissue make it an ideal tool for congenital disorders of the spine. Complete imaging of the spinal cord is required to ensure the recognition of multiple “skip” lesions and the hindbrain herniation seen rarely in patients with lipomyelomeningocele and myelocystocele.⁹¹

T1-weighted images provide clear anatomical detail of the spinal cord and filum terminale, allowing visualization of the vertebral level of the conus; the presence or absence of fat within the cord, spinal canal, or filum; and the size of the filum. T2-weighted images allow the identification of spinal cord tumors such as dermoids and epidermoids. In addition, they highlight intramedullary fluid-containing structures such as syringes, myeloceles,⁹² and neurenteric cysts.

The assessment of the filum terminale in patients suspected of having tethered cord syndrome has been difficult, particularly in the situation in which the filum appears normal and the conus terminates at a normal level. With the improvements in imaging resolution, the ability to recognize abnormalities in the structure of the filum has also improved. The majority of patients with a thickened filum have fat and fibrovascular tissue on histologic examination.⁹³⁻⁹⁵ Fat in the filum is always found at the junction of the filum with the caudal dural tube and involves more of the rostral filum in individual patients. If the filum immediately caudal to the conus is free of fat for 13 mm or more, it appears that symptomatic cord tethering is unlikely.⁹⁶

A variety of MR imaging sequences have been developed to evaluate cord motion, with the ultimate goal of being able to predict which lesions will require surgical untethering and to assess postoperatively the effectiveness of such procedures.^{51-53,97} Unfortunately, the goal of being able to use MR imaging to predict which patients will require untethering has not yet been achieved.

25.5.2 Ultrasonography

The role of ultrasonography in the evaluation or follow-up of patients with suspected closed spinal dysraphism is limited. Although it allows the operator to appreciate cord motion, its lack of spatial resolution limits its ability to define the causes of cord tethering. Despite these limitations and because of its low cost, ease of use, and minimal sedation requirements, ultrasonography has been used as a screening tool^{65,92,98,99} for

asymptomatic infants with sacral dimples or isolated strawberry hemangiomas in whom the findings of a normal conus location, “normal” filum, and normal filum, conus, and root motion would allow the clinician to postpone MR imaging. In each of these situations, the probability of cord tethering/OSD is known or presumed to be low.^{26,95} However, when a diagnosis of OSD is suggested by clinical or other radiographic findings, or when the study is inadequate for technical reasons, spinal MR imaging is required, in particular to show subtle anatomical lesions. Ultrasonography has a specific role to play in the assessment of myelocystocele in infancy. The meningocele and myelocele fluid spaces are easily resolved, and the continuity of the myelocele with the central canal can be confirmed by gentle ballottement of the postsacral mass. This finding can be used to differentiate myelocystocele from lipoma of the conus.

25.5.3 Urodynamics

The objective monitoring of bladder function is often fraught with difficulty of interpretation, especially in infants and children, because cooperation with the study is an intricate component of the evaluation. The usefulness of urodynamic studies lies in the following: (1) the evaluation of patients who are being assessed for incontinence and whose imaging studies are normal,^{86,87,100} (2) the monitoring of neurologic function when a nonoperative approach has been elected for an infant or child with conus lipoma,⁵ and (3) the comparison of function before and after surgical untethering. A validated scoring system has been developed that describes urodynamic abnormalities in children.¹⁰¹

Significant derangements in filling capacity, pressure, compliance, and contractility are found in patients with OSD.¹⁰² Improvement has been demonstrated postoperatively.^{28,86,103} The use of urodynamic testing in the preoperative evaluation of patients and in the postoperative, long-term follow-up of selected patients is recommended.

25.6 Treatment

25.6.1 Natural History and Surgical Decision Making

Randomized studies comparing the natural history of OSD defects with clinical outcomes after operative intervention have been conducted infrequently.^{104,105} In part, this is due to the fact that historically, the disparate conditions grouped as OSD were viewed as having natural histories, surgical outcomes, and operative risks that were of similar magnitude regardless of the etiology. As a result, assumptions regarding the effects of cord tethering and the presumed long-term benefit of operation were generalized to a varied group of pathologic entities. Because the risk for operative neurologic injury is low in many entities, and because clinically apparent “neurologic deficit” is more common in older children, early operation, before the development of deficit, was recommended as a standard for all forms of OSD.

With the improvements in imaging and with further clinical experience, it has become apparent that the forms of OSD differ markedly in the ease and safety with which they can be surgically treated and in the effectiveness of surgery to address

present and future clinical symptomatology (see box “Signs and Symptoms of OSD”). Surgery can address mass effect and in most cases cord tethering, but it does not address congenital myelodysplasia or predictably reverse established clinical defects.^{5,9,106–108}

The underlying OSD state is of critical importance in determining (1) the evolution of symptoms and signs, including their clinical presentation; (2) the natural history, including that which is due to myelodysplasia, mass effect, and tethering; and (3) the safety and long-term efficacy of surgery. Both historical and contemporary surgical series demonstrate that patients' symptoms and signs are more likely to be recognized as they age.^{104,105,109,110} They also demonstrate that deficits (musculoskeletal, neurologic, and urologic) are more likely to improve or be reversed if appropriate treatment for the cause of deterioration is undertaken in a timely fashion following the onset of the deficits. Unfortunately, in many patients, it is not possible to determine whether a deficit is truly new and has a surgically treatable cause or whether it is due to congenital myelodysplasia that becomes evident as development progresses. The assumption that all children are normal and that deterioration is the result of surgically correctable lesions has led to the conclusion that patients with OSD, if untreated, will progressively lose neurologic function with time. This thesis also assumes that the risks of surgery are minimal and that the efficacy will be long-lived.

In general, simple OSD responds predictably to surgical intervention, whether for untethering (tract excision, excision of tethering bands, filum section) or tumor excision. As the operative procedures are in most situations straightforward, the intervention can be done with a low risk for neurologic injury.^{5,7,8,106,111–116} Unfortunately, this assumption is not true for patients with complex OSD and may not be true for those with simple forms that may retether symptomatically.^{117,118}

25.6.2 Results of Surgical Treatment

The probability that a patient will recover from neurologic, urologic, and musculoskeletal symptoms varies with the cause of the symptoms and their duration. In general, a patient with fixed deficits or complete neurogenic bladder dysfunction does not recover as a result of operation, whereas a patient with progressive, evolving defects of musculoskeletal or neurologic function does recover to some degree. In the complex forms of OSD, a single untethering is not necessarily curative, and recurrence of similar or different symptoms is to be expected over the lifetime of the patient.^{5,7,9,106}

Urologic dysfunction often improves after an OSD untethering operation.^{27,86,87,119–123}

Back and leg pain is almost always relieved postoperatively.^{5,15,27,30,123,124}

Scoliosis responds differentially in simple and complex OSD. In the former, scoliosis if minimal will resolve with untethering, but complex OSD, in particular SCM, may be associated with structural vertebral anomalies that lead to progression.

The intraoperative risk for neurologic impairment, most commonly to bladder function, is less than 10%, with acute risk to sensory and motor function less for initial untethering operations.

25.6.3 Preoperative Evaluation

Routine preoperative laboratory testing and MR imaging of the spine comprise the usual evaluation before surgery. Spinal computed tomography (CT) can be very helpful in determining the challenges to laminectomy and lateral resection to provide access. Urodynamic testing is useful in determining the preoperative urologic status.

25.6.4 Intraoperative Neurophysiologic Monitoring

The purpose of intraoperative electrophysiologic monitoring is to distinguish between functioning nerve roots and spinal cord tissue and nonfunctional tethering structures that can be sectioned, thus minimizing neural injury.¹²⁵ Three main electrophysiologic techniques have been used in the operating room: (1) tibial and peroneal somatosensory evoked potentials (SSEPs), which theoretically detect excessive traction or lateral pressure on the conus; (2) pudendal sensory evoked potentials, which detect injury to the S2–S4 segments (which are very vulnerable to injury during an untethering procedure and are below the stimulation territories of the standard lower



Fig. 25.12 Intradural view of a markedly thickened filum infiltrated with fat in a child presenting with back pain, scoliosis, and enuresis.

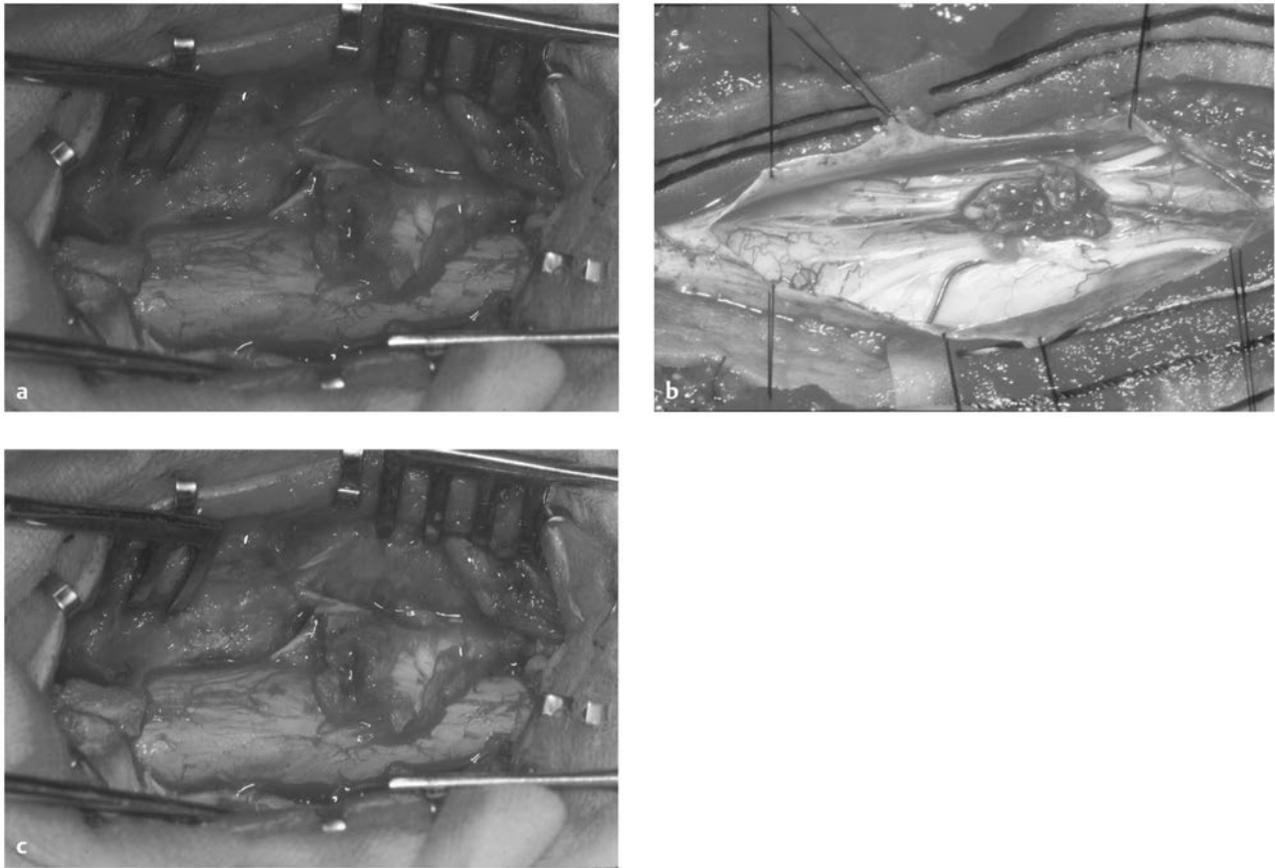


Fig. 25.13 (a) Extradural view during dissection of a type 1 split-cord malformation. Laminectomies have been completed on either side of the septum. Dysplastic spinous processes mushroom over the septum and adjacent laminae. (b) Dura opened and septum exposed. (c) Septum resected and cord untethered. Note the dysplastic dorsal roots in the split.

extremity SSEPs); and (3) free running electromyograms from lower extremity musculature including the anal sphincter and (4) uni- and bipolar stimulation of cord, roots, and/or tethering structures. Motor evoked potentials can be used to assess the effects of dissection on the cord.⁴⁵ Electrophysiologic improvement following surgical untethering can predate clinical recovery.¹²⁶

25.6.5 Surgical Technique

A *tight filum terminale* is approached through a laminectomy, laminotomy, or laminoplasty extending from S1 to the mid sacrum (► Fig. 25.12) or through the L5–S1 interlaminar space. Exposure of the distal 2 or 3 cm of the subarachnoid space is all that is needed to allow adequate exposure.¹²⁷ After the dural and arachnoidal opening, the filum is recognized by its posterior/midline location, the bluish discoloration, the absence of nodes of Ranvier, its vasculature, and the fat commonly seen infiltrating the structure. The filum is separated from surrounding roots, then rotated to ensure that there are no nerve roots adhering to the undersurface. The filum is then coagulated and divided, first proximally, then distally, if a specimen is to be sent for histologic evaluation. The cut ends of the filum infrequently retether,^{117,118,128} making the long-term outcome excellent.

The surgical management of SCM is based on the concept that the median septum is a tethering entity that should be removed. This is true whether the median septum is bony, fibrous, or cartilaginous (► Fig. 25.13). Before resection of the median septum and adhesions in a patient with type 1 SCM (diastematomyelia with septum) and kyphoscoliosis is undertaken, careful study of the spinal images, including three-dimensional CT scans, can be very helpful in that orientation of the hemicords relative to the surgical approach is fully appreciated. Great care must be taken while the laminae are removed because of the possible presence of transdural bands attached to the dorsal cord and the base of the bony septum. In type 1 SCMs, the septum is resected extradurally with rongeurs or a drill under magnification. The septum usually contains blood vessels that bleed briskly as bone is removed. The septum in SCMs usually occurs at the caudal end of the cord split, leaving the more rostral aspect of the split free of attachments. The free zone rostrally is a safe starting point for the resection.⁴⁵ Working in this safe zone, the surgeon resects the septum and the dural sleeve flush with the ventral surface of the canal. This opens the two dural tubes and permits a complete intradural exploration for tethering bands or dysplastic roots. Unless the two hemicords are widely separated, the ventral dural defect is not repaired. The dorsal dural defect created by the excision of the septum and its sleeve is repaired. The risk for neurologic injury

is highest during (1) the definition and removal of the deformed laminae and the spinous process(es) and (2) the removal of the dural sleeve. Preoperative surgeon orientation to the hemicords minimizes this risk. Symptomatic retethering is rare, although kyphoscoliosis may progress and require spinal fusion.

Split-cord anomalies without an osseous or cartilaginous median septum (type 2 SCMs) require exploration throughout the entire length of the split. The laminectomy and dural opening are less technically challenging. The fibrous septum is disconnected from the ventral dura by gently rotating the hemicords to one side, or by working between the two hemicords. Retethering is rare.

Meningocele manqué is tethered by dorsal band(s) that attach to the inner surface of the dura or pass through the dura to attach to the undersurface of the lamina. Occasionally, the dorsal bands are composed of nerve roots coming from the medial aspect of a split-cord anomaly. When these course dorsally and *not* ventrolaterally, they should be cut to allow total relaxation of the cord. If any question arises as to the functional nature of these elements, electrophysiologic stimulation may be useful. Long-term follow-up has shown that the majority of patients remain stable or improved. Associated lesions may be the reason for deterioration.³³

A *dermal sinus tract*¹²⁹ should be surgically explored and removed to its terminal insertion. Although occasionally it may seem to end at the dural surface on imaging studies, an intradural exploration is always warranted.³⁴ Insertion of the tract into an extraspinal *dermoid cyst* requires complete resection of the cyst. When the dermoid tumor is embedded within the conus medullaris, complete excision is technically difficult without incurring a neurologic deficit (► Fig. 25.4). In addition to their mass effect, dermoid cysts cause neural compression because of secondary infection within the dermal contents (intratumoral abscess). If an infection (meningitis or abscess) is present at the time of diagnosis and neurologic function is preserved, surgical exploration for excision may be delayed until the acute infection subsides.¹³⁰ In the face of progressive neurologic deterioration due to cauda equina and/or cord compression, intraspinal exploration is appropriate for abscess drainage and/or excision of the abscess or tumor.

25.6.6 Postoperative Care

Postoperatively, patients are nursed in a flat position to minimize orthostatic pressure of the CSF on the dural closure. This may not be possible for neurologically intact, active older infants, especially those undergoing untethering for simple OSD malformations. These children are allowed up in a parent's arms to settle. Patients are discharged on postoperative day 1 or 2. Foley catheters are inserted only in patients with a pre-existing neurogenic bladder, those undergoing untethering for complex OSD, or those harboring a tumor. It is removed postoperatively, and intermittent catheterization is started if the residual volumes exceed normal amounts. A short course of perioperative steroids may be administered to patients undergoing intramedullary surgical manipulation (complex OSD and dermoid cyst excision).

Tissue fluid or CSF leakage and seroma/pseudomeningocele are the most common nonneurologic complication of untethering.¹³¹ In the absence of infection, the fragility of the dura and

the need for dural grafts likely underlie these problems. Meticulous surgical technique in dural and wound closure usually suffices in most patients.

25.6.7 Retethering

The probability of retethering depends on the underlying OSD malformation, the surgical procedure undertaken, and whether postoperative meningitis or wound infection was present. Surgeons debate the role of graft material. The extent to which each of these parameters affects the retethering rate is unknown. Retethering after division of the filum terminale was thought to be rare; however, its occurrence is increasingly reported.^{117,118,128} The rate of retethering of more complex malformations is much higher and depends on the duration of follow-up.^{4-7,9,27,91,106,109,116,132,133}

Patients who experience late deterioration should undergo a repeated clinical and imaging evaluation to determine the cause. Possible causes include the development of a syrinx, retethering, and missed diagnoses or complications. Repeated untethering should not be limited to the lysis of adhesions. Other dysraphic lesions, previously undetected, should be sought and treated appropriately. Meticulous surgical technique plays a significant role in minimizing future arachnoiditis and retethering. Using a capacious dural graft tends to minimize the intradural crowding of tissues,¹³⁴ minimizing bleeding into the subarachnoid space tends to reduce the amount of arachnoiditis, and avoiding injury to or coagulation of the pial surface decreases the likelihood of the pia adhering to surrounding tissues. In general, the risks for further neurologic compromise and operative injury during repeated untethering operations exceed those risks at the time of the initial intervention.

25.6.8 Follow-up

Patients should be followed for the possibility of recurrent symptoms. They are usually evaluated in a neurosurgery or spina bifida clinic at 2 months following the procedure and yearly thereafter. Unless a syrinx is present, MR imaging is not repeated in asymptomatic patients. Patients with abnormal urodynamic studies preoperatively or those in whom abnormal bladder function develops postoperatively are evaluated with further urodynamic studies until the clinical and urodynamic measurements are shown to be normal. Scoliosis and genitourinary, neurologic, and bony abnormalities are addressed in the follow-up visits.

25.7 Conclusion

OSD comprises a constellation of spinal cord malformations that present with cutaneous, orthopedic, urologic, or neurologic dysfunction. These malformations cause traction on the spinal cord, which in turn causes ischemia as well as focal trauma to the cord and resultant neurologic deficits. The diagnosis is confirmed by MR imaging. The treatment of OSD should be based on a clear understanding of the underlying anomaly, its natural history, the etiologies for the patient's symptoms, and the risk and efficacy of surgical intervention. Operative intervention has been shown to halt the progression of symptoms in many patients, and to produce neurologic improvement in some.

Recurrence of symptoms and/or worsening disability is possible, and patients with OSD are best followed in a comprehensive, multidisciplinary clinic whose physicians have experience treating similarly affected children.

Pearls

- The cutaneous marker seen in an infant with OSD commonly predicts the underlying spinal cord abnormality.
- All newborns should be examined for dermal sinus in the immediate postnatal period. If a sinus is found, the high risk for meningitis requires that the patient be referred for imaging and excision of the sinus and any associated dermoid or epidermoid tumor before being discharged to home.
- The diagnosis of tethered cord syndrome should be considered in all patients with secondary incontinence regardless of whether the imaging findings are abnormal.
- All patients with caudal agenesis or hypogenesis should undergo imaging of the spinal cord to define any cord abnormalities.
- The imaging of patients with OSD must include all spinal levels and the craniocervical junction because multiple abnormalities are common and may be discontinuous. All lesions may require surgical treatment. When a lesion above the conus is explored (e.g., for an SCM), the MR images should be studied closely to assess the need for division of the filum terminale. If this is deemed necessary, the filum may need to be exposed through another incision or an extension of the same incision.
- Spinal cord ultrasound can be used in infants younger than 6 months of age to screen for many of the intraspinal abnormalities seen in OSD. MR imaging of the neural elements provides a definitive diagnosis, and CT will clarify the relationships of neural elements to osseous structures.
- Care must be taken in removing the lamina during OSD surgery. Dorsal bands originating from the dura or spinal cord may insert on the under surface of the lamina.
- To be considered pathologic (i.e., tethered), a conus at a normal level should be accompanied by objective findings of OSD, such as lamina defects, cutaneous signatures, or neurologic defects. Attention should be paid to the presence or absence of fat in the caudal filum.

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26 Surgical Management of Complex Spinal Cord Lipomas

Dachling Pang

The partial resection of complex spinal cord lipomas is associated with a high rate of symptomatic recurrence due to re-ethering.¹ Since 1991, the author has performed more than 330 total or near-total resections of complex lipomas with radical reconstruction of the neural placodes, designed to minimize the preconditions of re-ethering. Twenty years of follow-up have proven the long-term benefits of this technique.^{1,2} I now strongly advocate for total resection of spinal cord lipomas and radical reconstruction of the neural placode over partial resection because aggressive surgery, contrary to traditional teaching, is safe and gives far better long-term progression-free survival.¹

The rationale for total lipoma resection is based on three hypotheses:

1. The high rate of symptomatic recurrence after partial resection is due to re-ethering.
2. Re-ethering is promoted by three factors: a tight content-container relationship between spinal cord and dural sac; a large, "sticky," raw surface of residual fat; and incomplete detachment of the terminal neural placode from residual lipoma.
3. Total resection can eliminate the factors conducive to re-ethering and thus reduces the probability of symptomatic recurrence.

The object of surgery is therefore to create conditions that will minimize re-ethering. The first condition relates to the fact that the normal spinal cord exhibits intradural motions to gravity and postural changes on ultrasonography and dynamic imaging.^{3,4} Reducing the content-container ratio and amplifying the degree of freedom of the cord within the dural sac must lessen re-sticking by limiting sustained contact between the cord and the dura, this sustained contact being intuitively a necessary condition preceding the formation of fibrous adhesions. To do this, the cord bulk must be drastically reduced. For large, rambling, "virgin" lipomas, this means resection of all or most of the fat down to the thin, supple neural placode. For redo lipomas, the hard, grasping cicatrix must also be removed. The aim is to render the thinnest, most pliant neural placode possible that can be atraumatically neurulated (sutured from pia to pia; see below) without distortion or strangulation to form a slender, round tube. (The term *neural placode* in lipoma is borrowed from the familiar essential element of an open neural tube defect [ONTD] to emphasise its equivalent "neural" nature once purified of fat. The synonymous use of the term in lipoma and ONTD is logical if one ponders the embryogenesis of the two entities (see below); the "placode" in each case represents the original embryonic neural plate blighted in its final completing process, one invaded by paraxial mesenchyme, the other thwarted in its midline dorsal fusion.) The raw, sticky lipoma bed is simultaneously concealed within the tube, and the sac is enlarged by a capacious dural graft. Finally, total resection also enhances the chances of terminal untethering.

26.1 Anatomy and Classification

In the literature, the nomenclature of spinal cord lipoma is imprecise and inconsistent. Here, we define the types of lipomas as follows:

26.1.1 Dorsal Lipoma

The lipoma-cord interface is entirely on the dorsal surface of the lumbar spinal cord, always sparing the distal conus (► Fig. 26.1). The junctional demarcation between the lipoma, cord, and pia, the *fusion line* (see below), can always be traced neatly along a roughly oval track, separating fat from the dorsal root entry zone (DREZ) and dorsal nerve roots laterally (► Fig. 26.2). The lipoma therefore never contains nerve roots. The lipomatous stalk runs through an equally discrete dorsal dural defect to blend with extradural fat. The uninvolved conus often ends in a thickened filum terminale.

26.1.2 Transitional Lipoma

The rostral portion of this type is identical to that of a dorsal lipoma, with a discrete fusion line and easily identifiable DREZ and dorsal roots. Unlike the dorsal type, however, which always spares the conus, the transitional lipoma then plunges caudally to involve the conus as the plane of the fusion line cuts ventrally and obliquely toward the tip of the conus, likened to making a slanting, beveled cut on a stick (► Fig. 26.3a). The lipoma-cord interface thus created may be undulating and tilted so that the neural placode is rotated to one side or even spun into a parasagittal edge-on orientation, but the neural tissue is always ventral to this interface (i.e., on the side of the nerve roots exit), and the DREZ and the nerve roots are predictably localizable lateral and ventral to the fusion line and therefore do not course through the fat (► Fig. 26.3b). There may or may not be a discrete filum. The dorsal dural defect extends to the caudal end of the thecal sac and may be much larger on the biased side.

26.1.3 Terminal Lipoma

Unlike the dorsal and transitional types, terminal lipomas insert into the caudal extremity of the conus without blending with the spinal cord or its root entry zones. All the sacral roots clearly leave the conus rostral to the lipoma, and in most cases the conus itself looks normal. The dural sac and the dorsal myofascial coverings are intact. The lipoma either replaces the filum entirely or is separated from the conus tip by a short, thickened filum.

The surgery for terminal lipoma is relatively straight forward and therefore beyond the scope of this chapter.

26.1.4 Chaotic Lipoma

This novel type is so named because it does not "follow the rules" of either the dorsal, transitional, or terminal lipoma. It

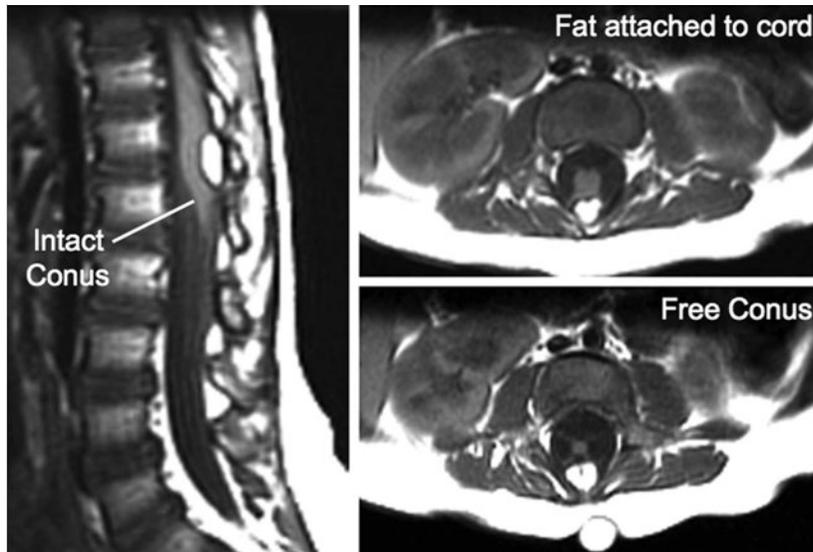


Fig. 26.1 Dorsal lipoma on magnetic resonance images. Sagittal image: Intact conus is caudal to the lipoma stalk. Axial images: Upper image shows site of lipoma attachment to cord; lower image shows free conus just caudal to the level of the lipoma attachment.

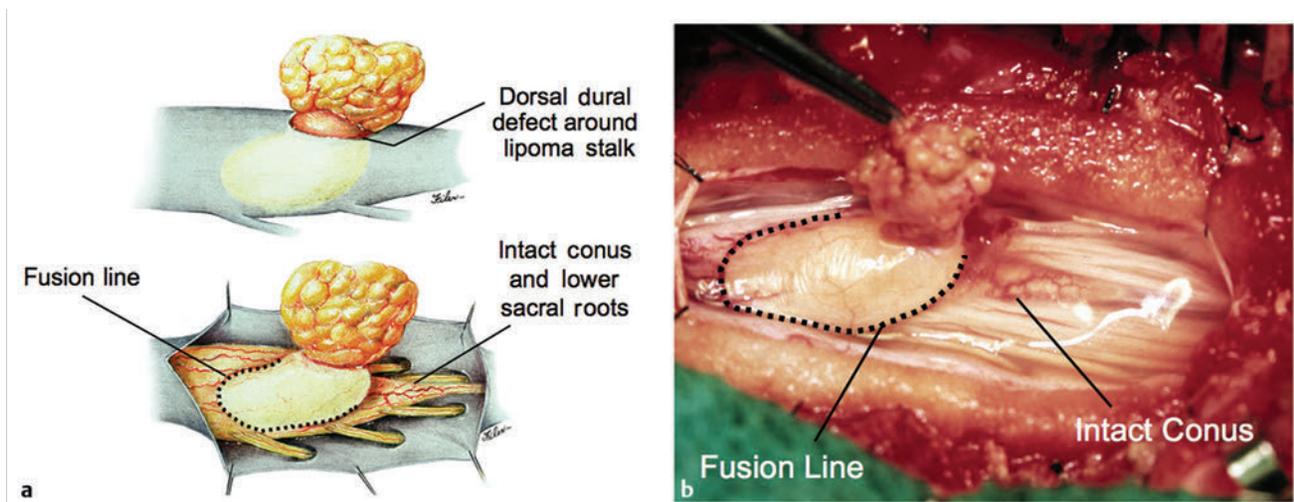


Fig. 26.2 Dorsal lipoma. (a) Intraoperative drawings show neat dorsal dural defect through which lipoma stalk goes. Lower drawing shows circumferential fusion line and intact conus. (b) Intraoperative picture shows neat oval fusion line around lipoma–cord interface in a horizontal plane. Note intact conus and caudal sacral roots.

begins dorsally in an orderly fashion, like a dorsal or transitional lipoma, but its caudal portion is *ventral* to the neural placode and does engulf neural tissue and nerve roots (► Fig. 26.4a). The fusion line may be distinct rostrally but quickly becomes blurred distally, and the location of the DREZ and nerve roots is less predictable. The moniker “chaotic” depicts the sometimes confusing blend of the ventral fat and neural placode, and the often impossible task of separating fat from neural tissue at surgery (► Fig. 26.4b). Chaotic lipomas are uncommon but are characteristically seen with sacral agenesis.²

The literature^{5,6} describes one other lipoma type, the lipomyelomeningocele, in which part of the distal conus extends into the extraspinal compartment, dragging with it a small collar of dural sac (► Fig. 26.5). The basic structure is that of either a transitional or a dorsal lipoma. Accordingly, we choose to classify this type as either a transitional or dorsal lipoma, with a descriptive qualifier of “extraspinal extension.”

26.2 Surgically Relevant Embryology

An understanding of the embryogenesis of lipomas is helpful in appreciating the surgical nuances.

26.2.1 Embryogenesis of Dorsal and Transitional Lipomas

In the embryo, a progressive disparity exists between the spinal cord and vertebral column as a result of the faster growth rate of the latter.^{7–10} The caudal end of the cord ascends gradually from opposite the coccyx in the 30-mm human embryo to the L1–L2 level at birth.^{9–12} Proper ascent of the cord requires a well-formed neural tube and a smooth pia–arachnoid covering. If during early development a dorsal defect exists in the dura

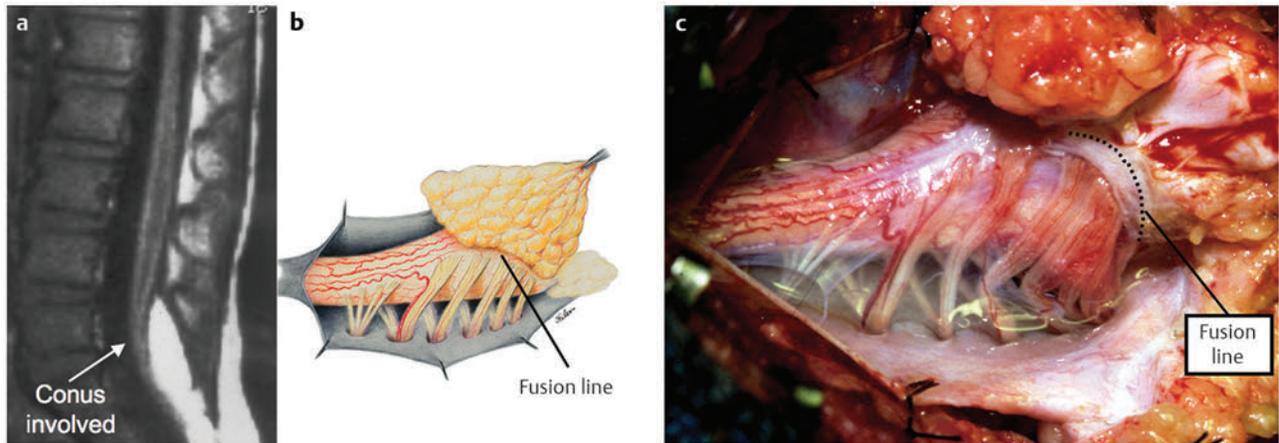


Fig. 26.3 Transitional lipoma. (a) Sagittal magnetic resonance image shows that lipoma begins dorsally but involves the entire conus. The ventral side of the neural placode is free of fat. (b) The plane of the fusion line begins dorsally, then cuts obliquely toward the tip of the conus. The array of DREZ and dorsal roots is also forced to slant dorsoventrally. (c) Intraoperative picture showing a massive lipoma but a very distinct dorsoventral fusion line separating fat from the DREZ and dorsal roots, which always lie lateral and ventral to the fusion line. The ventral side of the placode is always free of fat in a regular transitional lipoma

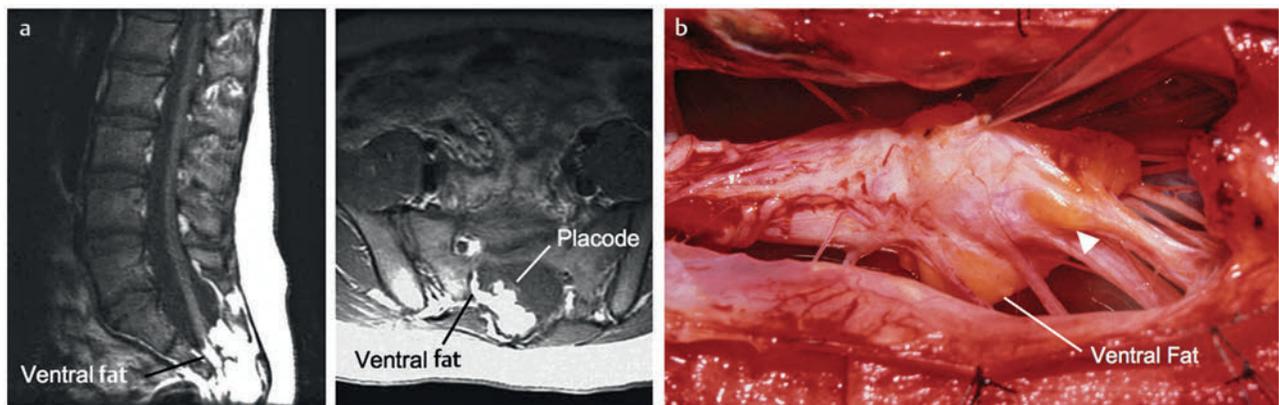


Fig. 26.4 Chaotic lipoma. (a) Sagittal magnetic resonance image shows ventral as well as dorsal fat in relation to the neural placode. Note sacral agenesis, with only two visible sacral segments. Axial image shows ventral fat and an extremely irregular lipoma-fat interface. (b) Intraoperative picture showing fat ventral to the placode and on one of the sacral roots (arrowhead). Note absence of a discrete fusion line.

(duraschisis) and neural tube (myeloschisis), mesodermal elements from the surrounding mesenchyme will enter the dural sac and form an attachment with the sliding neural tube in the form of a fibrofatty stalk, resulting in its entrapment. This theory features a fundamental defect in neural tube closure during primary neurulation (secondary neurulation does not involve dorsal neural fold closure), and thus it applies only to dorsal and transitional lipomas (see below). It is compatible with the observation that these two types of lipomas are always associated with neural arch defects.

Normal separation of the cutaneous ectoderm and neuroectoderm (disjunction) occurs *after* dorsal neural folds fusion, so that the surrounding mesenchyme is permanently segregated from the dorsal (ependymal) surface of the neural plate. The embryologic error leading to the mesodermal invasion of the neural tube probably lies in *premature disjunction* between the cutaneous and neural ectoderm^{13,14}, i.e., the separation of one from the other occurs *before* the converging neural folds fuse

with each other. This allows the paraxial mesenchyme to roll over the still gaping neural folds and enter the central canal. Once contact between the mesenchyme and ependymal neuroectoderm is made, further closure of the neural tube is permanently prevented, and a segmental dorsal myeloschisis is created (► Fig. 26.6a,b). Alternatively, the fault may lie in a delay in neural folds fusion secondary to an insufficiency of the paraxial mesoderm in impelling their dorsal convergence,¹⁵⁻²¹ so that ectodermal disjunction again precedes neural folds fusion. Lastly, faulty fusion of the neural folds due to a metabolic disturbance of the cell membrane-bound glycosaminoglycans, which are vital to cell-cell recognition and adhesion,²²⁻²⁵ can likewise reverse the temporal relationship between disjunction and neural folds fusion.

Experimental studies show that the pluripotential mesenchyme forms derivatives according to the inductive properties of the adjacent neuroectoderm (► Fig. 26.6c).^{26,27} The ependymal side of the neural tube induces mesenchyme to form fat,

muscles, collagen, and occasionally bone and cartilage, whereas the outer surface of the neural tube induces the formation of meninges.²⁸ However, no dura can now form over the dorsal opened portion of the neural tube, and the dural defect neatly surrounds the evolving lipomatous stalk, which tethers the neural tube to the subcutaneous adiposity. In like manner, deficiencies in the overlying myofascial layers (from myotomal mesoderm) and neural arches (from scleromesoderm) also neatly surround the lipomatous stalk (► Fig. 26.6d).

Within the neural tube, the intramedullary fat and muscles fuse with the developing alar and basal plates. Because the dorsal root ganglions develop from neural crest cells at the outer aspect of the neural fold lateral to the site of failed fusion, the dorsal nerve roots grow outward ventrolateral to, *but never traverse*, the lipomatous stalk. The DREZ must correspondingly lie very near, *but always lateral to*, the exact junctional boundary between the lipoma and spinal cord. This boundary, called the *fusion line*, is of tremendous surgical significance^{2,29,30} (► Fig. 26.6d). Meanwhile, the cutaneous ectoderm, long

detached from the neuroectoderm, heals over in the dorsal midline to form healthy skin over the subcutaneous lipoma.

The genesis of dorsal lipoma perfectly exemplifies mistimed disjunction during *primary* neurulation. Its fibrofatty stalk always involves cord segments above the conus, which forms mainly from secondary neurulation. Furthermore, the failure of primary neural tube closure appears to be *segmental*, and normal closure takes place—business as usual—immediately following the abnormal event. This “square pulse” nature is illustrated by the fact that the sharp fusion line between fat, spinal cord, and pia-arachnoid can be neatly traced circumferentially around the lipomatous stalk^{29–31} (► Fig. 26.2). Dorsal lipomas therefore result from a segmental closure abnormality *involving only primary neurulation*. They accounted for fewer than 15% of spinal cord lipomas in our series.^{1,2}

In transitional lipoma, the myeloschisis involves much more than an isolated segment of the primary neural tube. Even though its rostral part resembles the dorsal lipoma, the involvement of the whole of the caudal spinal cord means that not only primary but also secondary neurulation has been profoundly disturbed by the mesodermal invasion. This is supported by the observations that in many transitional lipomas, the filum is incorporated into the distal fat, and within the lipomas are often spaces resembling the vacuoles found within the secondary neural tube during its cavitory phase. Also, whereas the rostral part of the transitional lipoma is always dorsal and aptly reflects premature disjunction of primary neurulation, the distal part involves the core of the conus, a situation compatible with misguided mesenchymal inclusion during the much less orderly events of secondary neurulation. Intramedullary mesenchyme may migrate within the neural tube after invasion and travel caudally across the boundary from the primary to the secondary neural canal since the two neural canals are in continuity.³² In fact, the hypothesis that the rostral part of the transitional lipoma arises from aberrant primary neurulation (involving only the dorsal cord) and the caudal part arises from abnormal condensation of the secondary neural cord (affecting the deeper central core of the conus) furnishes at least one explanation for the

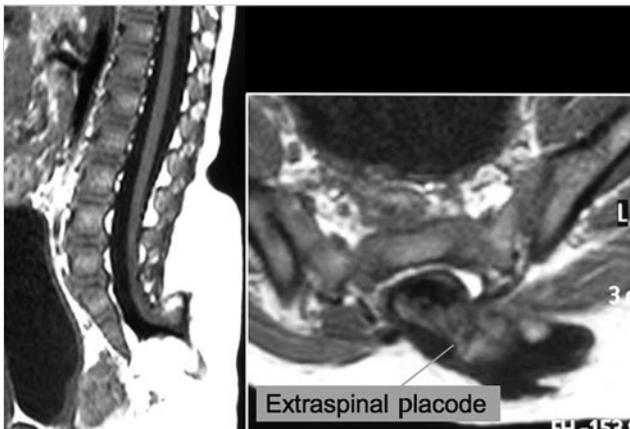


Fig. 26.5 Transitional lipoma with extraspinal extension (“lipomyelomeningocele”). The lipoma, cerebrospinal fluid sac, and part of the neural placode extend out of the spinal canal through a dorsal defect.

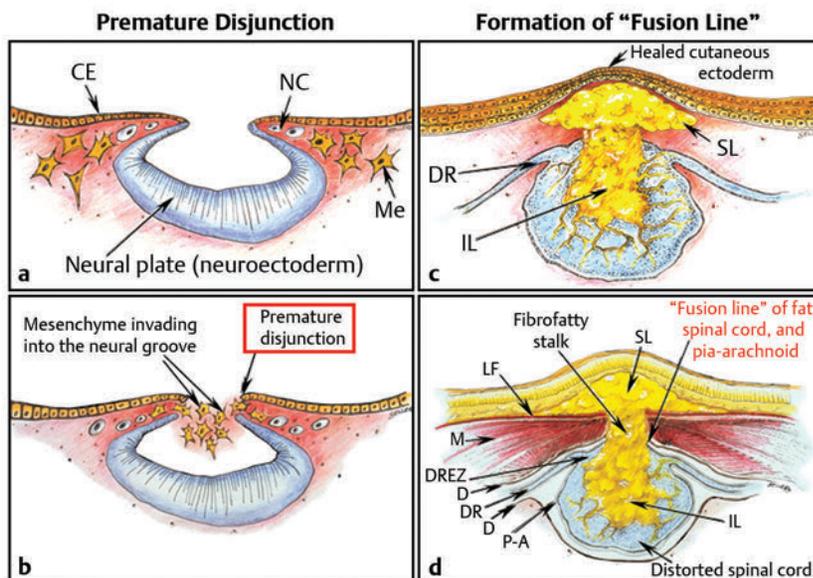


Fig. 26.6 Embryogenesis of a dorsal lipoma, a purely primary neurulation defect. (a,b) Premature disjunction before complete closure of the neural plates allows the migration of mesenchymal cells into the neural groove to be in contact with the ependymal surface. (c,d) Formation of a fusion line between the lipoma, cord, and pia-arachnoid. The DREZ and dorsal roots are always lateral to the fusion line and thus not entangled in fat. CE, cutaneous ectoderm; NC, neural crest; Me, mesenchyme; SL, subcutaneous lipoma; DR = dorsal root; IL, intramedullary lipoma; DREZ, dorsal root entry zone; D, dura; P-A, pia-arachnoid; M, muscle; LF, lumbodorsal fascia.

dorsoventral obliqueness of the lipoma–cord interface. Despite the larger field of involvement of the neural tube, the lipoma–cord interface remains relatively distinct in a transitional lipoma.

26.2.2 Embryogenesis of Chaotic Lipomas

Chaotic lipomas do not quite fit into either the dorsal or the transitional schema. They often do not have a distinct dorsal part with the symmetry of a dorsal lipoma, and the lipoma–cord interface is irregular and ill defined, with fat running through the neural placode to the ventral side in large and unruly measures. Even in the context of the less orderly transitional lipoma, the interplay between lipoma and cord in this type of lesion seems to be in constant chaos.

This degree of anatomical unpredictability in chaotic lipoma and its strong association with caudal agenesis (82% in our series²) suggest that the embryogenetic error occurs during the early stage of secondary neurulation as part of the general failure of the caudal cell mass (► Fig. 26.7).^{33,34} Secondary neurulation comprises three distinct stages: (1) condensation of neural material from the caudal cell mass to form the solid medullary cord; (2) intrachordal cavitation of the medullary cord^{32,34,35} and its integration with the primary neural tube; and (3) partial degeneration of the cavitory medullary cord through massive apoptosis to result in the thin filum terminale.^{9,32} It is possible that formation of the chaotic lipoma involves the entanglement of lipogenic mesenchymal stem cells with cells from the caudal cell mass during aberrant condensation of the medullary cord, forming an inseparable mixture of neural tissue and fat, with nerve roots projecting out haphazardly.²

26.2.3 Embryogenesis of Terminal Lipomas

Terminal lipomas result from abnormal *secondary* rather than primary neurulation, as evidenced by the unexcepted rule that the lumbar and upper sacral cord segments, products of

primary neurulation, are never affected in a terminal lipoma. Furthermore, dorsal myeloschisis and duraschisis, both hallmarks of failed (primary) neural fold fusion, are never seen. Lastly, the terminal lipoma either replaces or forms part of a thickened filum, which temporally places the pathogenetic process at secondary neurulation. The fact that the distal conus in terminal lipomas always remains fat-free argues against an abnormal condensation phase during early secondary neurulation. On the other hand, the terminal lipoma often contains (disorganized) spinal cord elements and ependymal tubules,^{36,37} which suggests rather an incomplete or ineffective degeneration phase at late secondary neurulation, possibly due to failed apoptosis.³⁸

26.3 Intraoperative Electrophysiologic Monitoring

Intraoperative monitoring has become a sine qua non in lipoma surgery.^{2,39,40} Elaborate electromyographic preparations are made to capture triggered motor responses from the relevant lumbosacral nerve roots. Standard electromyographic needles are inserted into the rectus femoris (L4), anterior tibialis (L4–L5), gastrocnemius (S1), and abductor hallucis (S2). Smaller-gauge (No. 27) electromyographic needles are inserted obliquely into the external anal sphincter through the anal verge on each side, which are insulated from each other by a plug of dry muslin gauze so that sphincter contractions from one side can be unequivocally distinguished from the other side.³⁹ All stimulations and recordings in our cases are done with the Cadwell Cascade Intraoperative Monitoring System (Cadwell Laboratories, Kennewick, WA) and the Cascade software version 2.0.

Stimulating needle electrodes are placed subcutaneously along the shaft of the penis in male patients and between the periclitoral skin and the labia minora in female patients. Stimulation of the sensory domain of the pudendal nerve via these electrodes generates an “electric” bulbocavernosus reflex, which is a form of H-reflex for the conus useful in monitoring the integrity of the central connections of the conus apart from motor root mapping.^{39,41}

- Associated with caudal agenesis
- Severe disturbance of caudal cell mass during medullary condensation Stage (1) of secondary neurulation

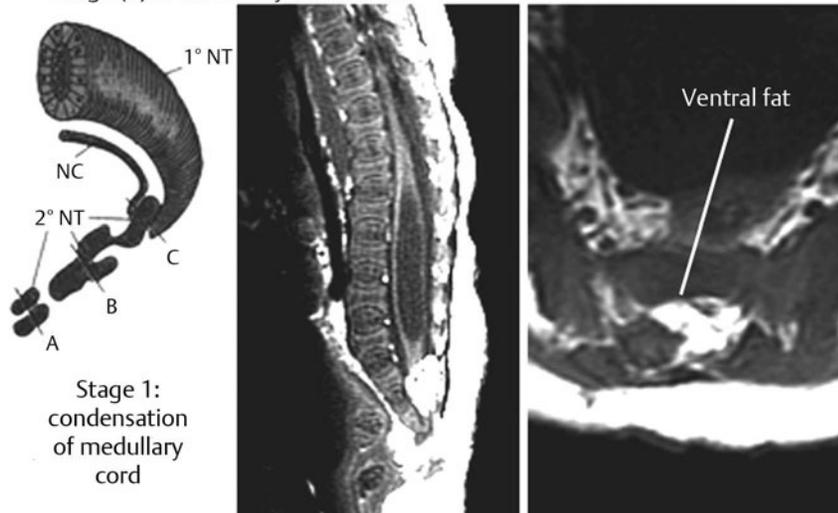


Fig. 26.7 Embryogenesis of chaotic lipomas. Left: Basic error probably occurs with the inclusion of abnormal lipogenic mesenchymal cells into the caudal cord during the condensation stage (stage 1) of secondary neurulation, with formation of the medullary neural cord, thereby generating fat tissue throughout the substance of the mature neural placode. Middle and right: Dorsal and ventral fat with associated sacral agenesis. 1° NT, primary neural tube; 2° NT, secondary neural tube; NC, notochord.

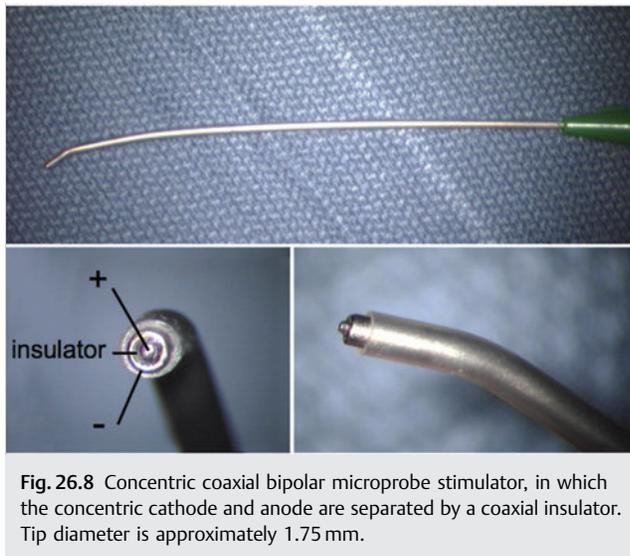


Fig. 26.8 Concentric coaxial bipolar microprobe stimulator, in which the concentric cathode and anode are separated by a coaxial insulator. Tip diameter is approximately 1.75 mm.

Standard stimulating electrodes are placed near the posterior tibial nerve behind the medial malleolus and near the common peroneal nerve at the fibular neck to enable somatosensory evoked potential monitoring for the spinal cord segments above S2.³⁹

All motor root and direct spinal cord stimulations are done with a concentric coaxial bipolar microprobe electrode that has an end plate diameter of 2 mm (► Fig. 26.8). The concentric configuration and small size of the anode–cathode complex allow extremely focused current delivery to a very small target volume, thus making the electrode ideal for the fine discrimination of small and crowded electroresponsive units.² Stimulating currents from 0.5 to 3.0 milliamperes are used depending on target impedance. The stimulation frequency is usually set at 10 per second. This permits spontaneous random firing due to nerve irritation from surgical manipulation to be distinguished from rhythmic evoked contractions.

26.4 Surgical Technique for Total or Near-Total Resection

26.4.1 Step 1. Exposure

The skin and soft tissue incision should go straight through the subcutaneous lipoma if one is present. Removing this will leave behind a large subdermal space into which cerebrospinal fluid (CSF) can collect under tension and consequently hinder wound healing. Frequently, a discrete fatty stalk connects the subcutaneous with the intraspinal lipoma through a defect in the lumbodorsal fascia. This stalk is continuous with the spinal cord and cannot be tugged on during fascial dissection.

The upper extent of the bony exposure should include one level above the rostral end of the lipoma. This reveals, for proper orientation, the “last” normal set of nerve roots and DREZ before the lipoma resection is started. Wide laminectomy is essential to afford full access to the lateral edges of the dural sac (see below). Visualization of the normal dura rostral to any lipoma gives a depth perspective as to how far out the neural tissue

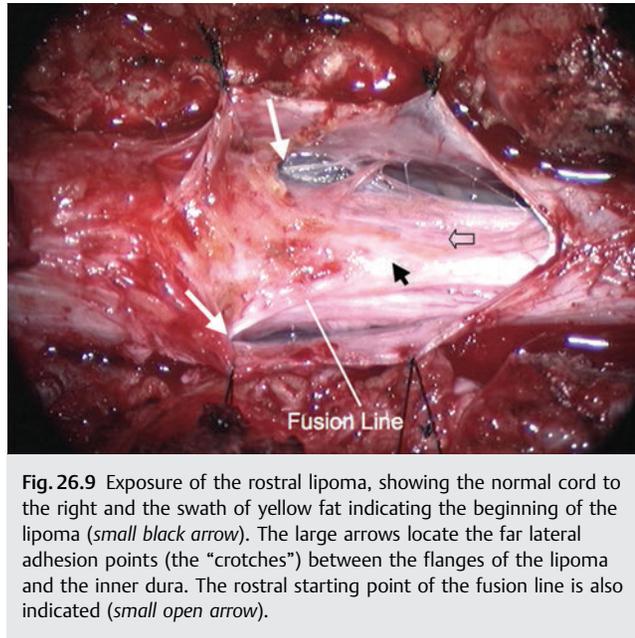


Fig. 26.9 Exposure of the rostral lipoma, showing the normal cord to the right and the swath of yellow fat indicating the beginning of the lipoma (*small black arrow*). The large arrows locate the far lateral adhesion points (the “crotches”) between the flanges of the lipoma and the inner dura. The rostral starting point of the fusion line is also indicated (*small open arrow*).

and CSF sac may have extruded beyond the plane of the dura. The heavy bulk of extradural fat can then be safely lopped off to give room for intradural dissection and lighten the tug on the conus.

26.4.2 Step 2. Detachment of Lipoma from Dura

The dura is always opened in the midline about 1 cm rostral to the lipoma regardless of whether it is dorsal or transitional. For a dorsal lipoma, the midline incision is then carried circumferentially around the discrete lipoma stalk and down the middle again to expose the conus (► Fig. 26.2a). For a transitional lipoma, the midline cut is carried right up to the lipoma, where the dura quickly thins out to nothing in the middle, although decent dura can usually be picked up just beyond the lateral edge of the lipoma stalk. Unlike with the dorsal type, the bifurcated dural incisions with a transitional lesion can seldom be made to rejoin neatly in the midline caudal to the lipoma stalk, usually not until the whole of the lipoma–placode complex had been exposed, many steps later (see below). At this stage, the freed-up portion of the dural edge on each side must be tautly and widely retracted with sutures. This is crucial maneuver because full lateral exposure of the intradural span, made possible by generous bone removal, reveals the “crotch” where the far lateral fringe of the lipoma attaches to the inner surface of the dura (► Fig. 26.9).

Next, the *fusion line* is identified, where the pia, spinal cord, and lipoma join in a continuous furrowed border that travels in a rostral to caudal direction, outlining the entire attachment of the lipoma stalk to the cord. In a dorsal lipoma, the fusion line forms a neat, *complete* oval or circle from side to side, usually upon a leveled horizontal plane, often bilaterally symmetrical, and always sparing the conus below (► Fig. 26.2a,b). In a transitional lipoma, the rostral fusion line starts distinctly enough but then edges ventrally toward the tip of the conus and tends

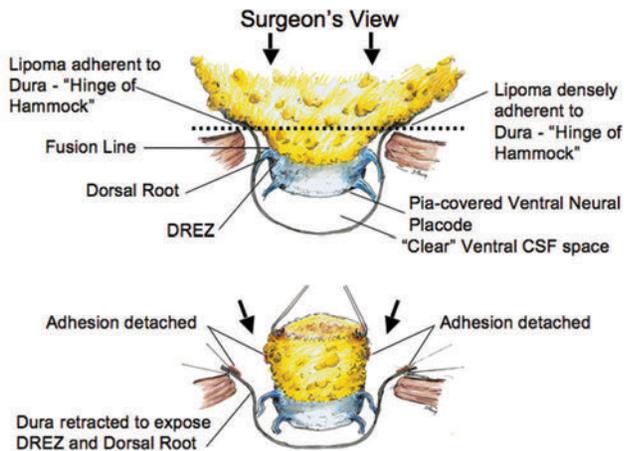


Fig. 26.10 Drawing depicting the relationships between the lipoma, neural placode, nerve roots, and dural sac in an axial slice. Upper: The lipoma-cord assembly is suspended at the dural edge at far lateral adhesion points, like a hammock against side hinges. The dotted transverse line that joins the two side hinges divides the assembly into a dorsal disorderly fibrofatty half that completely blocks the surgeon's view and a much more orderly ventral half containing the important anatomical landmarks of the fusion line, DREZ, dorsal roots, fat-free ventral placode, and pristine ventral cerebrospinal space. Lower: After the far lateral adhesion points (the hinges) have been detached by careful "crotch dissection" and the fatty mass has been folded in, the ventral anatomical landmarks can be visualized.

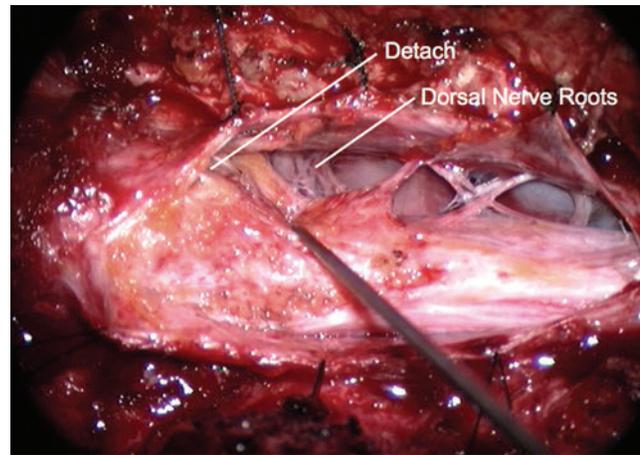


Fig. 26.11 Step 2 of surgical technique, "crotch dissection," in which the far lateral adhesion points between the fringes of the lipoma and the inner dura are sharply detached to unhinge the hammock of the lipoma-cord assembly. Note how the proximal sets of dorsal roots are revealed with just the first efforts to unhinge the hammock.

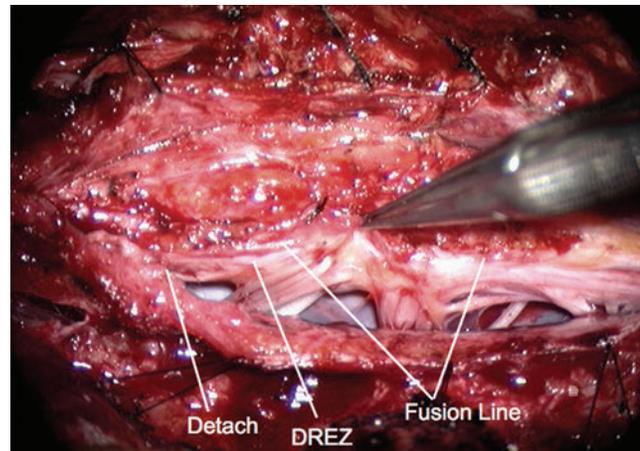


Fig. 26.13 Exposure of all relevant anatomy vital to the next stage of the actual resection of the lipoma: the fusion line, DREZ, dorsal roots, ventral side of the placode, and free cerebrospinal fluid space, in dorsal to ventral order. DREZ, dorsal root entry zone.

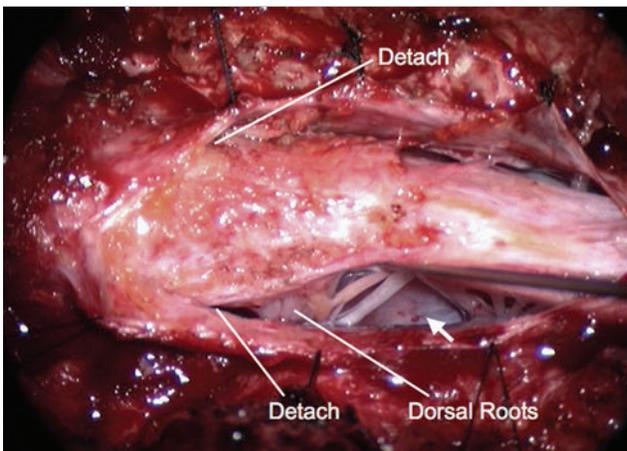


Fig. 26.12 Exposure of the pristine ventral cerebrospinal fluid space (arrow), nerve roots, and fat-free ventral side of the neural placode.

to wander laterally and asymmetrically, often becomes sheltered by the overhanging fat, and never meets its counterpart from the other side at the caudal end (► Fig. 26.3a,b).

True to the events of embryogenesis, the DREZ and dorsal roots are always lateral to the fusion line, and at the rostral end of the fatty stalk of both lipoma types, this orderly arrangement can be depended upon on both sides, thus presenting a convenient place at which to start the dissection. In most transitional lipomas, however, the more caudal nerve roots are quickly covered from view by the overflowing fat, which tends to fuse with the dura at a far lateral point (► Fig. 26.10 upper). Hence the

use of the term *crotch dissection*, which depicts the key step of grasping the overhanging fat and pulling it medially under tension against the tagged dural edge, then sharply separating the fat-dura attachment with the dissecting scissors (► Fig. 26.10 lower and ► Fig. 26.11). It is absolutely essential to lean the round curve of the scissors firmly against the inner lining of the dura while this attachment is cut to avoid blindly injuring the nerve roots, which project from the cord slightly medial to the "crotch" and lie just deep to the fat. The hidden roots should spring into view wherever the detached fat is pulled back, and they can be gently coaxed away from the dura by blunt dissection toward the exit foramina (► Fig. 26.12). At the same time, the free CSF space ventral to the dorsal roots and the fat-free, pia-covered ventral surface of the neural placode, hitherto hidden by the overhang, now "pop" into view (► Fig. 26.13).

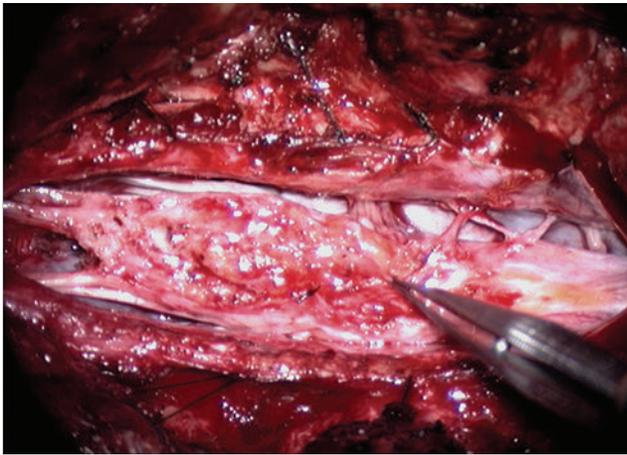


Fig. 26.14 Complete bilateral detachment of the adherent hinges and terminal untethering; the neural placode now “sinks” into the basin of the dural trough.

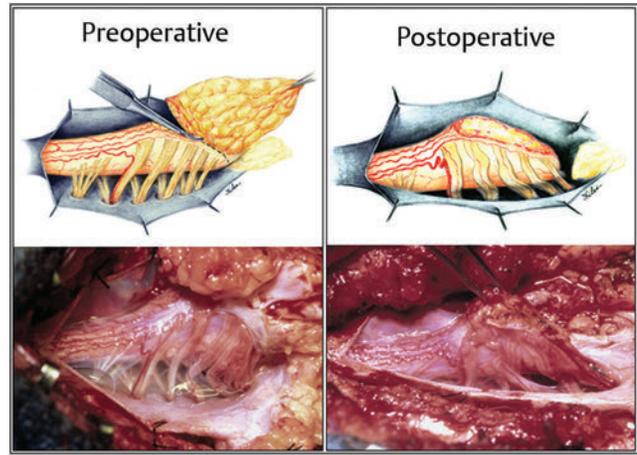


Fig. 26.15 Basic technique for transitional lipoma resection on an asymmetric and oblique fusion line along an occasionally undulating lipoma–cord interface plane, showing pre- and postoperative pictures.

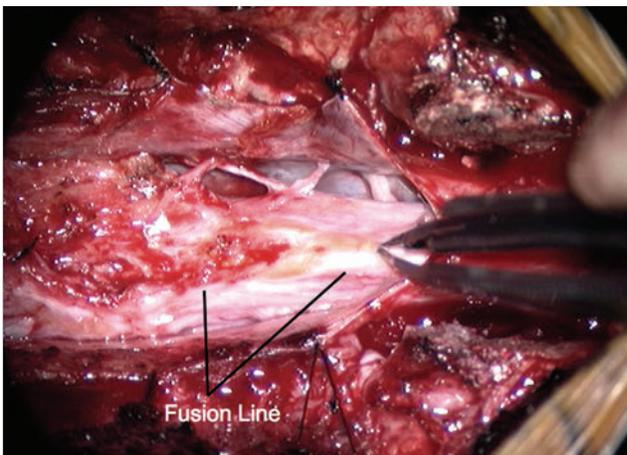


Fig. 26.16 Step 3 of surgical technique. Resection of the lipoma begins at the rostral end of the fat, at the semilunar edge showing just a small yellow swelling (at the points of the bipolar microforceps). Note the rostral fusion line and first pairs of dorsal roots.

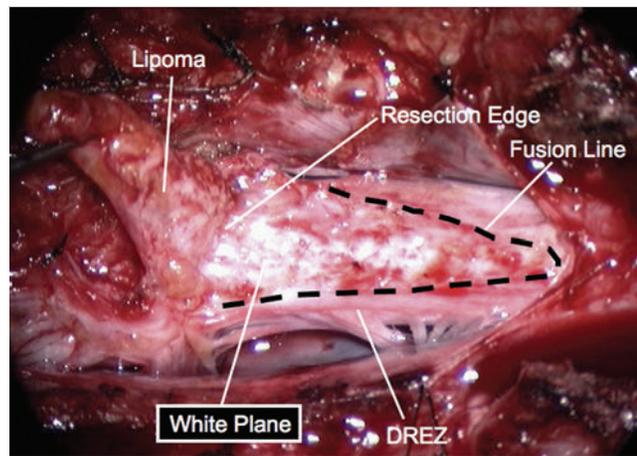


Fig. 26.17 The “white plane” of thin, glistening, fibrous netting separating fat from spinal cord, bounded always by the fusion line. Note the detached rostral portion of the lipoma lifted away from the white plane to show the resection edge. DREZ, dorsal root entry zone.

It is clear from this description that in each successive axial slice, all lipomas, big or small, dorsal or transitional, are roughly divided by a transverse line joining the points of the far lateral fat–dura attachment on each side, where the lipoma–cord assembly is in effect suspended like a hammock against two lateral hinges over an uncluttered ventral CSF pool. Dorsal to this transverse line is the visible but disorderly, massive, and unrevealing fat, and ventral to this line are the orderly fusion line, DREZ, dorsal nerve roots, neural placode, and ventral CSF space, but all initially made invisible to the surgeon by the overhanging fat (► Fig. 26.10 upper). The purpose of the “crotch dissection” is therefore to release this suspension so that the hammock of neural placode and nerve roots can be folded inward enough to be identified and preserved during the next phase of lipoma resection (► Fig. 26.10 lower).

This laborious but indispensable step of “crotch dissection” is carried all the way caudally (► Fig. 26.13) until all the “useful”

nerve roots are identified and the entire neural placode, with a profusion of lipoma still attached, is completely unsuspected from the dura and has literally “fallen” into the basin of the dural trough (► Fig. 26.14).

26.4.3 Step 3. Lipoma Resection

Resection of the lipoma begins at the rostral end, where the anatomical relationships between fat, DREZ, and nerve roots are clearly decipherable (► Fig. 26.15 and ► Fig. 26.16). Sharp dissection with microscissors is used to locate a thin but distinct silvery *white plane* between fat and cord at the demilune of the rostral fusion line (► Fig. 26.17). It takes some determination, for the initiate, to cut into this traditionally forbidden place, seemingly straight into the spinal cord right at the fusion line, but with experience, this white plane can be found in every case. We strongly discourage using the carbon dioxide

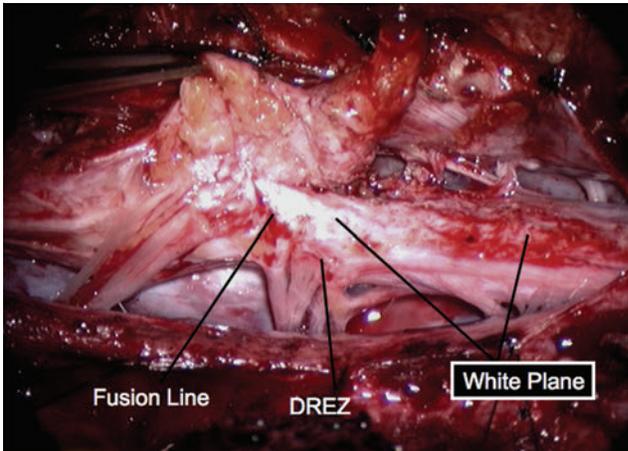


Fig. 26.18 At the outer margin of the white plane, dissection is kept strictly on the fusion line, thus reliably sparing the slightly more lateral DREZ and dorsal roots. DREZ, dorsal root entry zone.

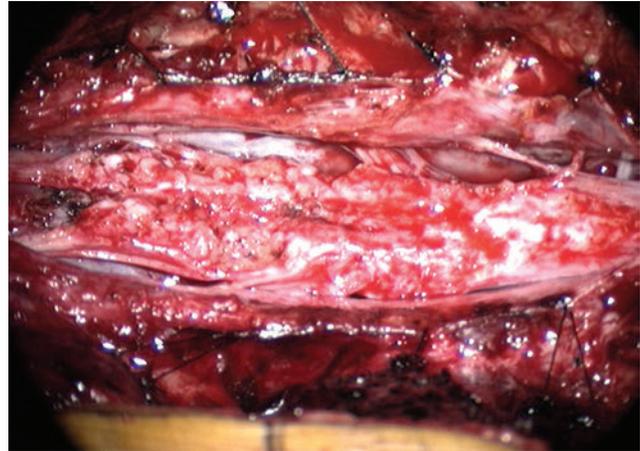


Fig. 26.19 Completed resection of a lipoma, leaving a thin, supple, purely neural placode free from all adhesions.

(CO₂) laser to vaporize the fat because it chars the surface and thus blurs the safety net of the white plane, and because of its hands-off nature, it does not provide the tactile feedback of the microscissors, on which the surgeon depends to differentiate between clipping the slight grittiness of fibrous fat, the tougher white plane, and the formless softness of the spinal cord. The neodymium:yttrium–aluminum–garnet (Nd:YAG) laser may produce slightly less blackening of the target surface but is hardly better in navigating the dissection plane, and it also lacks contact feedback. Bleeding on the white plane can be handled with the ultrafine irrigating bipolar cautery (0.2-mm tips) and a very low current setting. The cold irrigation mitigates against sticking, but more importantly, it dissipates heat rapidly from the cord. Minimal diathermy is used on the DREZ to avoid post-operative dysesthesia.

As long as all the activities are carried out medial to the fusion line, and thus also medial to the DREZ and nerve roots, dissection along the white plane can be conducted safely all the way to the end with no damage to the cord or nerve roots (► Fig. 26.18 and ► Fig. 26.19). In a dorsal lipoma, this is a simple feat because the white plane is basically horizontal and flat, the two banks are symmetrical, and the caudal end is well defined rostral to the conus, so that a completely circumscribed attack on the fat is possible from multiple angles (► Fig. 26.20). In a large transitional lipoma, navigating the white plane is more difficult because it always slopes ventrally and often undulates, and one side may be tilted so steeply that the corresponding DREZ and nerve roots are shifted ventrally and the placode so rotated that its ventral surface now faces the side. Such a white plane is almost turned vertically “on edge,” and its orientation is confusing unless one remembers the transverse line concept of dividing a “clean” ventral hemisphere from a “messy” dorsal one.

The white plane sometimes seems to be never-ending in large transitional lipomas, and the caudal thecal sac is thronged with fat admixed with suspicious strands. This is when systematic stimulation and identification of the ventral nerve roots become invaluable in localizing the termination of the *functional* spinal cord. The S2 ventral root is readily identified when both the anal sphincter and the abductor hallucis contract on appli-



Fig. 26.20 A dorsal lipoma can be resected with a completely circumscribed perspective from all sides of the fusion line.

cation of a low current of 0.3 to 1.0 milliamperes, and the next two sets of caudal rootlets with a “pure” sphincter response are thus S3 and S4. As soon as these sphincter roots are found and preserved, the tissue distal to the last “live” pair can be considered nonessential and can be cleanly cut across to achieve the final liberation of the placode (► Fig. 26.21b). A good chunk of the now isolated distal fatty stump should be excised to prevent reconnection with the terminal placode.

In chaotic lipomas, electrophysiologic determination of the functional extent of the neural placode may be the only way to achieve final untethering; the caudal fat–cord–fibrous jumble can be sorted out only functionally and not anatomically, by direct stimulation of the placode and the projecting nerve roots. The handling of the white plane on the dorsal side of a chaotic lipoma is the same as with the other lipoma types, but the billows of fat on the ventral side of the placode should be left alone and its smooth pial surface left unviolated (► Fig. 26.21). It is always the dorsal and never the ventral part (unless iatrogenically invaded) of the lipoma that actually tethers the spinal cord.²

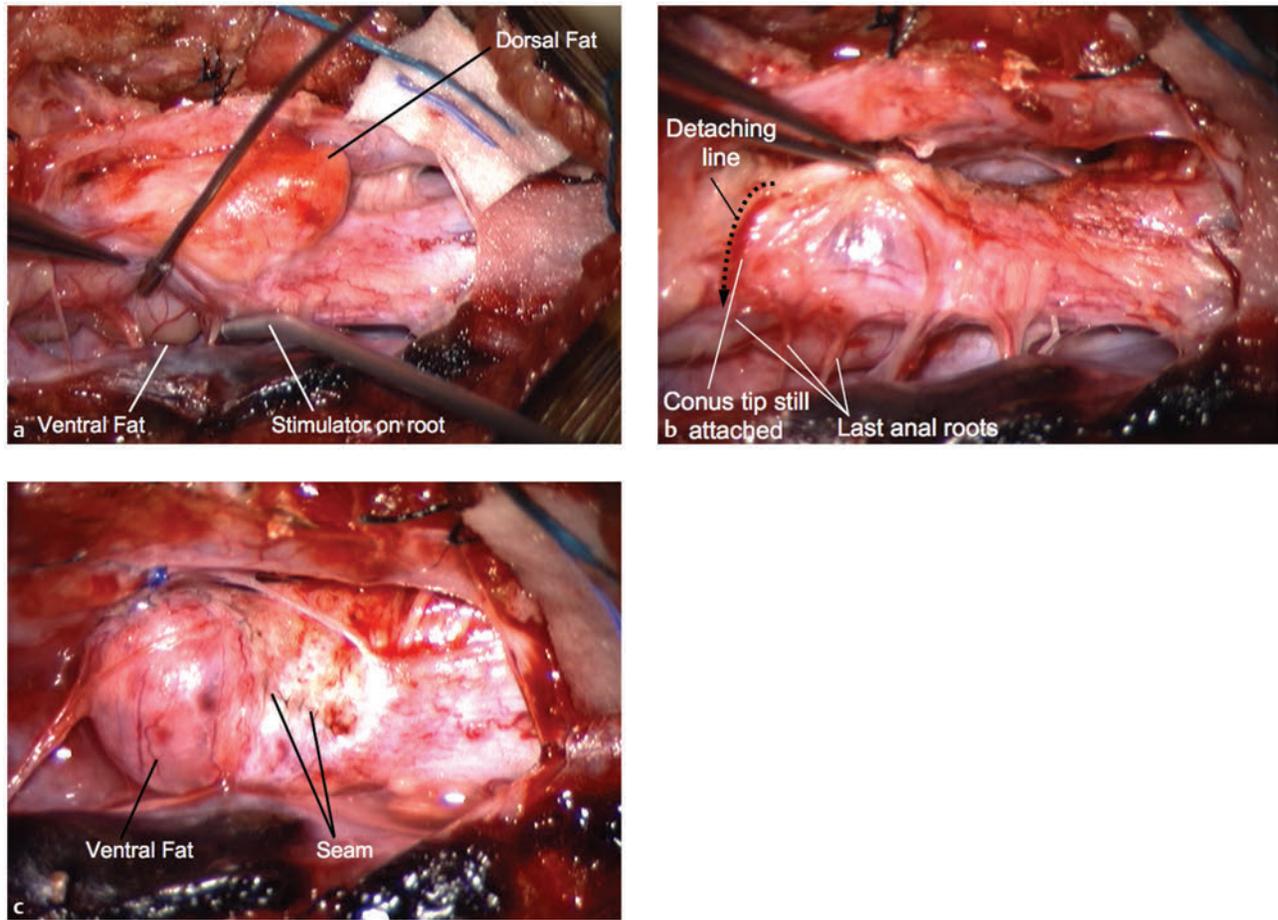


Fig. 26.21 Chaotic lipoma. (a) Note the ventral pia-covered fat medial to the ventral nerve roots (being stimulated by the concentric microprobe) and the dorsal fat located on the dorsal side of the placode. (b) Terminal disconnection of the neural placode from the residual caudal lipoma stump after identification of three healthy pairs of anal sphincter motor roots. (c) Caudal placode pulled up dorsally widthwise, to be neurulated with the more proximal pial edge to form the seam, displaying the unviolated pia-covered ventral fat as a blunt stump.

26.4.4 Step 4. Neurulation of the Neural Placode

Total resection of the dorsal fat and thorough unhinging of the placode convert a bulky, transfixated lipoma–cord complex into a free-floating, thin, supple, purely neural plate (► Fig. 26.19), eminently suitable for pia-to-pia, midline dorsal closure with interrupted 8-0 nylon sutures without strain or strangulation to the neural tissue (► Fig. 26.22a). It is helpful to leave a narrow cuff of pia along the cut edges of the white plane to accommodate the sutures, which are tied with inverted knots. Neurulation thus transforms a broad, waferlike, sticky sheet into a trim, sturdy, pia-covered tube bearing a single seam, evocative of the natural neurulation process (► Fig. 26.22b).

26.4.5 Step 5. Expansile Graft Duraplasty

The argument for a graft dural closure comes from the belief that if the neurulated placode could slosh about in ample CSF

within a capacious sac, the likelihood of reattachment to the dura would be diminished. The choice of graft material is based on two important criteria: its texture and its propensity to leak CSF at the suture holes. Gore-Tex (W. L. Gore, Newark, DE) is too stiff for infant dura and leaks badly, so it was discarded in our early trials. CSF also regularly oozes through DuraGen (Integra, Plainsboro, NJ). Autologous fascia lata, once a popular option, is so soft and pliant that it swells and ebbs with respiration and body movements, and during its in-phase it almost completely collapses onto the neural placode. Thus, we prefer the slightly full-bodied yet texturally compatible (with infant dura) bovine pericardium (Dura-Guard; Synovis, St. Paul, MN), which can maintain a “puffed-up” shape at all times and does not leak. A close second choice is Durepair (Medtronic Neurologic Technologies, Goleta, CA), which is made of reconstituted collagen matrix from bovine skin rather than straight bovine pericardium; it is only slightly stiffer than Dura-Guard and also does not leak at suture holes. The bovine graft is carefully measured and shaped to prevent inward folds. Running Prolene sutures are used to achieve a watertight closure, which is confirmed with Valsalva maneuvers (► Fig. 26.23).

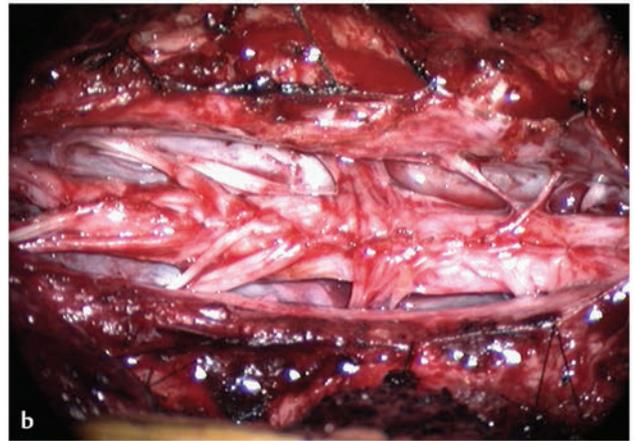
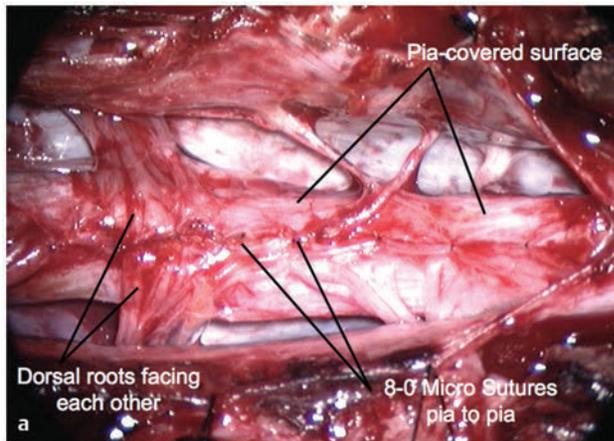


Fig. 26.22 Step 4 of surgical technique. (a) Pia-to-pia neurulation with 8-0 nylon sutures tied with inverted knots. Reconstituted neural tube is now completely covered with pia, and the dorsal root entry zones on each side are once again facing their opposite counterparts near the midline. (b) Completed neurulation.



Fig. 26.23 Step 5 of surgical technique. Completed expansile graft duraplasty with bovine pericardium.

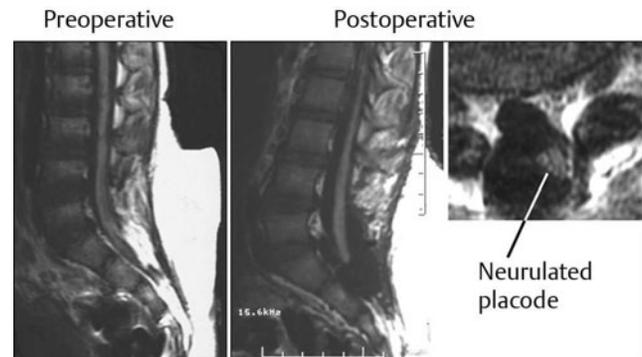


Fig. 26.24 Pre- and postoperative magnetic resonance images of a transitional lipoma with no residual fat after total lipoma resection. Note the neurulated oblong fat-free neural placode within a large dural sac.

26.5 Technical Points

Our data show that a total or near-total resection of spinal cord lipomas can be done in more than 90% of cases² (► Fig. 26.24). In most instances, a small amount of residual fat is adherent to the DREZ and has been invaginated out of mischief during neurulation (► Fig. 26.25). In the 8% of patients with an unusually large amount of residual fat, the fat belongs to the ventral component of a chaotic lipoma and has been intentionally left pia-covered and therefore harmless.

To assess the “looseness” or degree of freedom of the reconstructed placode within the newly formed dural sac, we created the cord–sac ratio, defined as the ratio of the diameter of the cord to the diameter of the sac on the postoperative axial MRI at the bulkiest portion of the reconstructed segment. The ratios are classified as low (<30%) in the loosest sacs, medium (30 to 50%) in moderately loose sacs, and high (>50%) in the tightest sacs (► Fig. 26.26). In the total group of 238 patients, 162 (68%) had low cord–sac ratios, 61 (25.6%) had medium ratios, and 15 (6.3%) had high ratios.²

The size of the lipoma is not an important determinant of the completeness of resection. Much more relevant is the

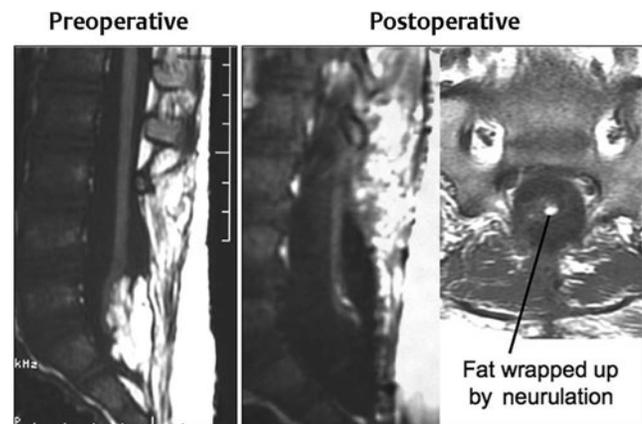


Fig. 26.25 Pre- and postoperative magnetic resonance images of a case of complex transitional lipoma with a very small amount (<20 mm³) of residual fat after resection. Axial image shows the small round piece of fat wrapped up within the roundly neurulated neural placode and therefore not exposed on the surface.

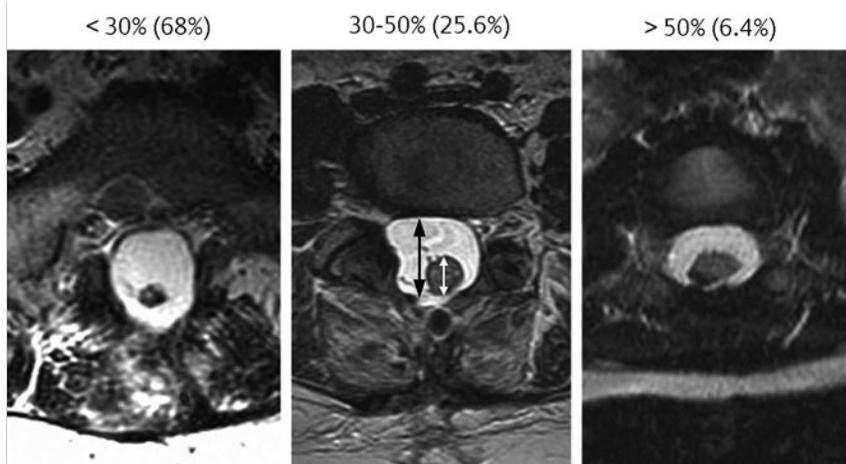


Fig. 26.26 Cord-sac ratios on the postoperative axial magnetic resonance images after total or near-total resection of lipoma. This ratio is obtained by dividing the sagittal diameter of the most bulbous portion of the post-neurulated neural placode by the sagittal diameter of the dural sac. In our series, 68% of the patients had very loose sacs (cord-sac ratios <30%), 25.6% had intermediate ratios (30 to 50%), and 6.4% had high ratios (>50%), with the least commodious cord-sac relationship. The cord-sac ratio estimates the degree of freedom of motion of the post-neurulated spinal cord within its container sac.

configuration of the lipoma-cord interface, which contains the “white plane.” The white plane is a filmy netting of relatively compact collagen fibers. It may be extremely contorted and asymmetric in some transitional lesions, and there is no better way than boldly cutting into the tongue of the rostral lipoma to find the glistening fibers beneath the first few globules of yellow fat. Once the plane is located, one can follow it with sharp dissection by feeling the grittiness through the microscissors and by spotting the glistening white stripes between yellow fat and pink spinal cord. With large dorsolateral transitional lipomas, the placode may be twisted 90 degrees, and the lipoma-cord interface can look almost vertical. Access to the DREZ of the ventral (down) side can be awkward unless the “hammock” is first unhinged and the placode is swung back to a more horizontal position. On the more involved side, festoons of overhanging fat may obscure the emerging dorsal roots to give the false impression that they *course through*, not underneath, the lipoma. In fact, this overhang can be readily teased and lifted off the “knee turn” of the dorsal rootlets to allow these to be traced under the veranda of fat into the true DREZ, at which site the white plane can once again be picked up. In general, a sinuous and severely rotated white plane makes it more likely that residual fat will be left behind.

Redo lesions are associated with a higher rate of residual fat and a higher cord-sac ratio. When the fat layer is infiltrated by a heavy cicatrix from previous surgery, the cementing hold to the surrounding dura is much more tenacious and harder to detach, and the bright yellow of “virgin” fat is lost to a gray, dense concretion that is much harder to distinguish from the white plane. The dissection is often stopped short of the white plane for fear of cutting too deep, and the result is a stiffer slab of residual scar-studded fat that not only augments the bulk of the placode, but also makes it awkward to fold at neurulation. The presence of this unyielding fat and scar at the DREZ often leads to “gouging,” which may well be the cause of postoperative dysesthetic pain in patients.¹

Incomplete terminal untethering of the placode predictably ends in a recurrence of symptoms.⁴²⁻⁴⁴ We ascribe two explanations for the surgeon’s hesitation to make the final disconnecting cut. With very large transitional lipomas, the distal neural placode is buried in fat, and unless visualization is improved by the substantial removal of fat, safe untethering cannot be done.

Also, nerve twigs are sometimes seen issuing in pairs from the distal placode, making it seem impossible to complete the detachment without sacrificing functional cord. This assumption is spurious, for as long as two or three anal sphincter-activating roots, presumably S2 to S4, are identified and preserved, there should be no loss of function if the terminal cut is made just *caudal* to these roots. The small nerve twigs within the discarded stump that do not respond to stimulation are probably coccygeal roots; these are vestigial in humans and have no essential function.^{1,2,45}

Thus, thorough lipoma and scar resection and terminal untethering impart the optimal bulk, texture, and maneuverability to the neural placode for tensionless neurulation. A low postoperative cord-sac ratio has been shown to be the single most important factor in securing a long-term progression-free survival (PFS) in lipoma surgery¹ (see below).

Finally, our experience unequivocally shows that chaotic lipomas are the most treacherous lesions. They can be recognized on preoperative MR imaging by the presence of ventral fat medial to the ventral nerve roots and by their association with sacral agenesis (► Fig. 26.21). Compared with other lipoma types, chaotic lipomas are more likely to show conspicuous residual fat and a high cord-sac ratio on postoperative MR imaging.^{1,2} The strategy for a chaotic lesion is knowing just when to stop excavating deeper after the dorsal portion of the lipoma has been removed to enable neurulation. If the ventral fat is judged not amenable to total excision and neurulation, then its pial surface that had hitherto lain freely against the adjacent ventral dura should be left untouched to avoid creating new adhesions (► Fig. 26.21c).

26.6 Complications

Our combined neurologic-urologic deterioration rate following total or near-total resection is 4.2%, which compares favorably with rates in the literature ranging from 0.6 to 10%^{5,6,44,46-59} and averaging 3 to 7%, associated with partial resection using more conservative techniques for partial resection. Only 1.7% of patients had new weakness, but about 4% had neuropathic pain, which, we suspect, was due to close encounters of the DREZ and dorsal roots with heat from the electrocautery. Most minor

bleeding on the cord can be stopped with gentle tamponade and Gelfoam, and if diathermy has to be applied, only the ultra-fine microtipped irrigating bipolar cautery should be used, with very low current intensity.

The CSF leak rate (0.8%) and wound complication rate (1.3%) with total resection are much lower than in almost all of the published series (of partial resections), which record CSF leak rates from 2 to 47%^{6,44,47,48,52–54,57,59} and wound dehiscence and infection rates of 2 to 26%,^{6,44,48,50,52,54,57,59} Good results can be attributed to the following technical stipulations: (1) Enough bony exposure must be done caudally so that a cuff of healthy dura *past* the lowest extent of the lipoma can be made available for graft anastomosis. The graft should never be sewn to the web of fat at the remaining lipoma stump. (2) Absolutely watertight closure of the graft with Prolene must be achieved and tested with Valsalva maneuvers. (3) Synthetic or organic tissue glues are used if there is even a suggestion of a leak. (4) In large sacral lesions, there are often gaping muscle and fascial defects that cannot be primarily approximated. In these cases, paramedian relaxing incisions can be used on the flanking lumbodorsal fascia to facilitate sliding midline closure of the myofascial edges.⁶⁰ A large subcutaneous lipoma is never removed at the time of intraspinal surgery. The creation of this immense dead space will encourage the collection of CSF, which may turn into an enlarging pseudomeningocele that compresses the dural graft back onto the cord and prevents the desirable “billowing effect” of CSF on the new thecal sac. A tense pseudomeningocele may even threaten skin flap viability.

26.7 Results of Total Resection

26.7.1 Early Postoperative Results

The early postoperative results were very similar between our total and partial resection groups.¹ For asymptomatic patients in both groups, the rates of neurologic preservation were 98% and 94%, respectively. In symptomatic patients who underwent total or near-total resection, 61% had a normal or improved neurologic status and 33% remained unchanged, thus giving a rate of 94% for improvement or stabilization of disease. In symptomatic patients who underwent partial resection, 33% were improved and 62% had disease stabilization, at least for the short term.

Our early postoperative results for total resection are thus comparable to or better than those in the literature, in which mainly reported partial resection.^{5,44,47,48,54,57,58} In particular, prophylactic total resection of asymptomatic lipomas carries a small neurologic risk when done by experts. Also, the benefits of radical surgery are obvious for patients with progressive deterioration. Finally, early improvement and stabilization rates are almost identical for total and partial resection, suggesting that the immediate benefits of surgery are due to the abrupt relief of traction on the conus and not to the extent of lipoma resection or placode reconstruction. Authors who specifically describe their inability to completely disconnect the conus from its caudal attachment owing to the presence of obscuring residual fat and an undelineated cord–lipoma margin also point out the corresponding poor outcome of these patient.^{6,42,44}

When the postoperative status of patients with total resection is correlated with preoperative symptoms, the best result is seen for pain. Most of the sharp, dysesthetic leg and perineal pain significantly diminishes within 3 months, but not necessarily low back pain, which is likely mechanical in origin.^{61,62} Children also become more active and playful, and virtually never have chronic back complaints. Sensorimotor deficits also respond favorably to surgery. Although fewer than 20% of patients have an actual normalization of motor function, the majority substantially improve.^{1,2} Like patients with other forms of tethered cord, those with milder and more recent deficits have a better chance for a good recovery. Bladder dysfunction responds favorably in about 20 to 30% of patients.² The subtype of neuropathic bladder with the best prognosis is the small-capacity, spastic bladder with uninhibited detrusor contraction. Atonic bladders seldom improve with surgery, and intermittent catheterization usually needs to be continued indefinitely. The response of detrusor–sphincter dyssynergia to surgery is unpredictable. It is mandatory that cystometry and voiding cystourethrography be repeated 3 to 6 months after surgery to determine what other urologic procedures, such as bladder augmentation and placement of ureteral conduits, may be necessary to prevent reflux and frequent infections. Surgery has been known to arrest the rapid worsening of existing scoliosis in patients with a tethered cord. However, severe scoliosis still requires surgical realignment and fixation with instrumentation and fusion.

26.7.2 Long-term Outcome

Whereas the *immediate* benefits of total lipoma resection are due to the abrupt cessation of spinal cord tethering and are thus comparable to those of partial resection,² the long-term advantage of total over partial resection becomes very obvious if the PFS of the two techniques are calculated for periods of 15 to 16 years. The PFS after total resection for all lipoma types and clinical subgroups is 84%, versus 34% for partial resection.¹ The differences in PFS are even more marked when the lipomas in each treatment group are segregated according to presence or absence of symptoms, patient age, and whether previous surgery was done.¹ The risk for symptomatic recurrence is 5.94 times higher after partial resection than after total or near-total resection over 12 years by the Cox proportional hazard regression model ($p < 0.00001$; ► Fig. 26.27). Even though the comparison is between prospective and retrospective data, the impressive difference in long-term PFS between the two techniques makes a compelling argument for endorsing total or near-total over partial resection.

The question is often asked whether surgery should be offered to children with asymptomatic lipomas. In 2004, a prospective study of the nonsurgical management of asymptomatic lipomas from l'hôpital Necker-Enfants malades, Paris,⁶³ reported an actuarial risk for deterioration of 40% over 9 years, with a PFS probability of 60%.⁶⁴ Given that children with lipomas have an actuarial life of 65 to 70 years, and given further that established neuropathic bladder and sensorimotor deficits seldom fully recover following *post factum* or salvage surgery,^{2, 5,28,39,62,66} the endorsement for prophylactic surgery seems attractive if it does in fact offer clear outcome advantage over conservative treatment.

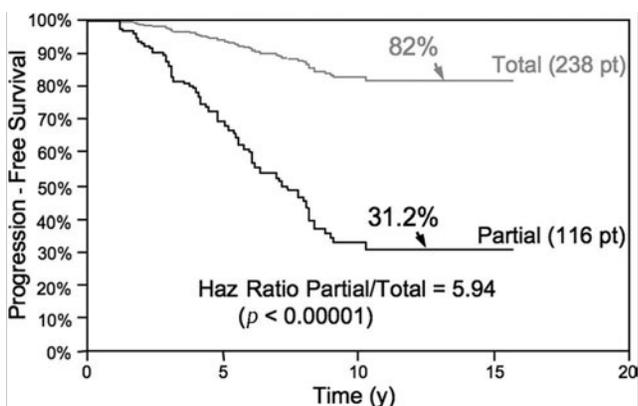


Fig. 26.27 Cox proportional hazard regression analysis of long-term outcome of total versus partial resection of lipomas.¹ Progression-free probabilities for the two treatment groups are indicated by arrows. The hazard ratio for symptomatic recurrence of partial to total is 5.94 ($p < 0.00001$). The advantage of total over partial resection is obvious. pt, patients; Haz, hazard; Partial and Total indicate extent of resection.

When the select group of young children without symptoms or prior lipoma surgery from our total resection series is put up against the Parisian series, the superiority of total resection is obvious, with a 16-year PFS of 98.4%¹ compared to 67% for conservative management⁶³ (► Fig. 26.28). Furthermore, there is a strong suggestion of stabilization of disease 5 years after total resection, whereas the probability of deterioration remains cumulative beyond 9 years with nonsurgical treatment.⁶³ These robust statistics argue strongly for total resection, not only for symptomatic patients but also as prophylactic treatment for all comers.

There are currently no longitudinal data on untreated asymptomatic lipomas in adults, and the actuarial life span for adults is obviously shorter, so a forceful argument cannot be made for prophylactic surgery in adults with lipomas. When a lipoma causes symptoms, however, it is widely assumed that deterioration will be inexorable, and aggressive surgery can be justified regardless of the patient’s age.

26.8 Cord–Sac Ratio and the Importance of Neurulation

Comparing our two series of total and partial lipoma resections, we found a steep bias for low cord–sac ratios with total resection, making cord–sac ratio the most likely factor that differentiates total from partial resection. That a low cord–sac ratio is an extremely important determinant of good outcome is amply supported by the Cox multivariate model, which shows that the cord–sac ratio exerts a highly significant, independent influence on outcome. This means that no matter how the associative influences of age, symptoms, lipoma type, and prior surgery reinforce or cancel one another, the influence of the cord–sac ratio stands solitary and undiminished (► Fig. 26.29). Thus, all other variables notwithstanding, a cord–sac ratio higher than 50% predicts a 5.6 times greater risk for disease progression than does a low cord–sac ratio of less than 30%, with a high statistical significance (► Fig. 26.30).

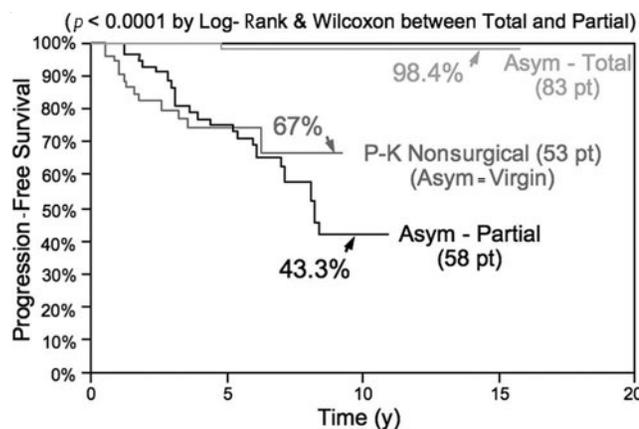


Fig. 26.28 Outcome differences between total resection, partial resection, and nonsurgical management of asymptomatic virgin lipomas by Kaplan-Meier analysis.¹ The nonsurgical survival function graph (P-K [Pierre-Kahn] Nonsurgical) from the Parisian study⁶³ is inserted for visual comparison only and is not meant to imply a true head-to-head comparison. Progression-free probability at 16 years for the 83 asymptomatic virgin lipomas that underwent total resection is 98.4%, much better than the 67% in the Parisian series and far superior to the 43.3% in our own partial resection series. The difference between total and partial resection for asymptomatic virgin lipomas is highly significant ($p < 0.0001$). pt, patients; Asym - Total, asymptomatic virgin lipomas treated by total resection; Asym - Partial, asymptomatic virgin lipomas treated by partial resection; P-K Nonsurgical (Asym - Virgin), asymptomatic virgin lipomas managed nonsurgically.⁶³

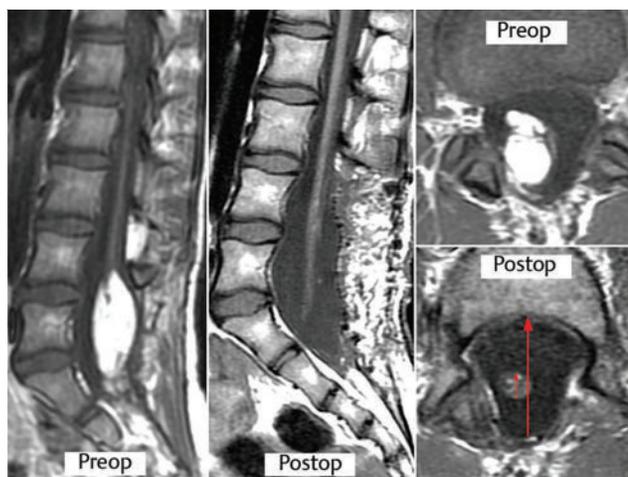


Fig. 26.29 The pre- and postoperative sagittal and axial magnetic resonance images of a 10-year-old girl who had undergone two previous partial resections of a large transitional lipoma and who was also highly symptomatic. The achieved postoperative cord–sac ratio was 20% (lower right), and she enjoyed long-term progression-free status.

In an operational sense, the cord–sac ratio may be thought of as the summated product of the other predictors. For example, previous surgery on the lipoma undoubtedly makes it much harder to achieve a small cord–sac ratio; the texture and hue of scar tissue within the fat can be confused with the white plane, leading to retention of excessive fat and cicatrix and a bulky

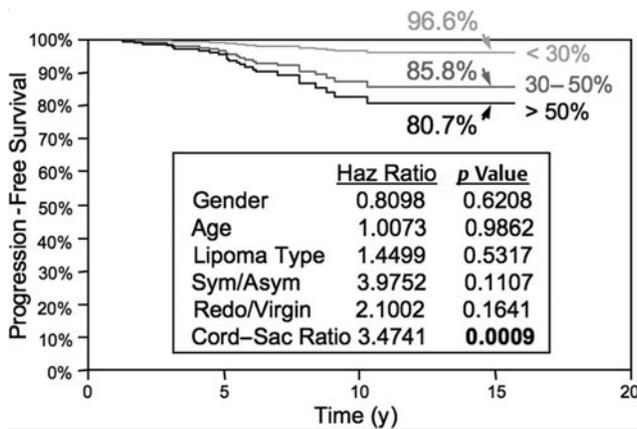


Fig. 26.30 Cox multivariate proportional hazard regression model analyzing the combined influence of six predictor variables (gender, age, lipoma type, symptoms, redo vs. virgin, and cord-sac ratio) on progression-free survival after total resection, featuring the resultant effect of the three cord-sac ratios of < 30%, 30 to 50%, and > 50%.¹ The hazard ratios and *p* values for all six predictor variables are listed in the miniaturized table, which shows that the cord-sac ratio exerts the only significant independent influence on outcome. The respective progression-free probabilities, indicated by the arrows, are 96.6% for low ratio, 85.8% for intermediate ratio, and 80.7% for high ratio. The differences in hazard prediction for the three ratios are highly significant (*p* = 0.0009, in boldface type). The ratios of < 30% to 50%, and > 50% indicate the three cord-sac ratios mentioned. Sym/Asym, symptomatic versus asymptomatic lipomas.

placode.² Since many of the symptomatic lipomas in our total resection group are redo lesions, their poor prognosis may in large part be due to the pre-eminence of the “redo factor.” This “redo factor” is likely also the underlying cause for the negative effect of age on outcome because older patients are more likely to be symptomatic and to harbor redo lesions.

Although a loose-fitting sac permits a greater freedom of cord motion within the CSF and is proven important in preventing retethering, adhesion to the dura can still happen if what remains exposed is a sticky, unneurulated, raw lipoma bed. Meticulous neurulation conceals this raw surface within an imbricated seam. Our experience of re-exploring unneurulated placodes leaves no doubt that this raw surface is a conspicuous focus of adhesion to the dura much more than a well-executed seam. Though not an easily quantifiable act, concealment of this adhesive surface through minutely careful neurulation must rank equally with a low cord-sac ratio as staunch insurance against retethering.

26.9 Is Partial Resection Worse than No Resection?

This is a prickly question because an affirmative answer seems self-serving in the present context, yet it would be disingenuous to ignore the fact that our results for partial resection of 116 lipomas^{1,2} are clearly worse than those in the Parisian series⁵⁴ of nonsurgical treatment. Even if we select only our asymptomatic patients, which in essence eliminates all the surgically more treacherous redo lesions, the PFS for partial resection is still only

43% at 11 years,¹ compared with 67% in the nonsurgical series⁶³ (► Fig. 26.28). Other series of partial resection do not fare much better. If the terminal lipomas were excluded, the series of Colak et al⁶⁵ would have a PFS rate of less than 50%, and the series of partial resection of Pierre-Kahn et al would have a PFS also lower than 40%.⁶ The transitional lesions of Cochrane et al⁴⁷ had only a 20% PFS over 10 years, and Cornette et al⁶⁶ reported a rapid progression of symptoms after partial resection.

We were impressed, after having tackled more than 100 redo lipomas, that a once-abraded but unneurulated placode can be much more firmly fused to the dura by unyielding scar than an unchastened lipoma stalk. If the likelihood of deterioration has to do with the rigidity of transfixation of the cord, one would anticipate partial resection to incur earlier and perhaps worse recurrence than if no surgery had been done. It would also explain why partial resection typically provides instantaneous relief of symptoms due to the *initial* untethering, but is unable to sustain this effect in the long run because of delayed scar formation. Ultimately, the patient experiences an increasingly failing course that compares poorly with the natural history of the disease.

26.10 Conclusion

The total or near-total resection of complex spinal cord lipomas and complete reconstruction of the neural placode produce a much better long-term PFS than partial resection. In comparing our own statistics with published data, we also found that total or near-total resection confers significantly greater benefits than nonsurgical management in the subset of patients with asymptomatic virgin lipomas. The postoperative rates of neurologic, urologic, and wound complications after total or near-total resection are either comparable to or much lower than those in other series reporting on partial resection.

Multivariate analyses show that a low postoperative cord-sac ratio and a well-executed neurulation of the neural placode are strongly correlated with a good long-term outcome. The ideal patient profile for early disease stabilization and the best recurrence-free survival has been identified to be a child younger than 2 years of age who is without symptoms or a history of previous surgery.

Based more on experience than on hard statistics is the impression that chaotic lipomas are the most difficult lesions to resect and may ultimately prove to be the most problematic type of lipoma. Also, there are strong indications that partial resection in some cases produces severe scarring at the lipoma-cord interface, which may actually worsen prognosis than if no surgery is done.

As a coda, I feel obliged to deal with the unceasing murmur that radical lipoma resection is too difficult and unlearnable. I suspect that the word *radical* may have an intimidating connotation that unintentionally deters attempts to explore even the basic brushwork. In truth, and as many observers of the operation can attest, a few specific maneuvers of total resection may be novel, but the fundamental microsurgical techniques are those taught in any modern neurosurgical program. In addition, the essential electrophysiology can be mastered by any trained neurophysiologist, and the monitoring hardware can be purchased at reasonable cost. Perfecting the procedure admittedly

takes arduous practice, but so does everything else in neurosurgery. Success in this endeavor ultimately depends more on a singularity of mind and granite tenacity, practicable by most, than on the sort of rarified technical wizardry inculcated by proponents of other revolutionary surgery.

Pearls

- Total or near-total resection of complex spinal cord lipomas and radical reconstruction of the neural placode can be done safely if one respects a few unique anatomical features and adheres to specific surgical principles.
- The long-term retethering-free probability for all lipoma types is much higher with total resection than with partial resection. Success is also strongly correlated with the postoperative cord–sac ratio and the state of neurulation of the neural placode.
- The long-term prognosis of total resection for the subset of children with asymptomatic virgin lipomas also far surpasses that of partial resection and the natural history of the disease. Total resection is recommended as prophylactic treatment for this subgroup.
- Partial resection has a much worse long-term outcome than no surgery for asymptomatic lipomas because of the creation of new scarring that causes more staunch tethering.
- Intraoperative electrophysiologic monitoring is an essential adjunct, especially for children who have large and complex lipomas with seemingly unending caudal involvement with fibrofatty tissue.
- The surgical and intraoperative physiologic monitoring techniques can be readily learned by anyone willing to do so, and the hardware can be purchased at a reasonable cost.
- Chaotic lipomas emerge as a small but problematic subset whose treatment demands special skill and perspective.

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27 Craniovertebral Junction

Arnold H. Menezes and Raheel Ahmed

A wide spectrum of congenital, developmental, and acquired abnormalities arises at the craniovertebral junction. These abnormalities are due to a complex developmental anatomy and to the neuroanatomical and musculoskeletal transitions between the brain and spinal cord and between the skull and cervical spine, respectively. Various craniovertebral pathologic conditions involve the osseous structures and encompassed neurovascular system, resulting in a constellation of signs and symptoms that often complicates diagnosis in children.^{1,2}

Historically, craniovertebral abnormalities have been defined through autopsy reports, followed by anatomical and embryologic studies and much later by radiographic imaging.³ Initial surgical treatments consisted of posterior decompression combined with occasional dorsal fusion. Advances in neurodiagnostic imaging and microsurgical instrumentation have improved our understanding of the biomechanical properties of this complex region and have enabled the effective treatment of a wider range of pathologic entities.^{2,4,5} Nonetheless, surgery at the craniovertebral junction is still considered a neurosurgical quagmire because of the associated high morbidity and mortality. In 1977, the senior author (A.H.M.) proposed a surgical physiologic approach to the treatment of abnormalities at the craniovertebral junction in children, based on an understanding of the dynamics, stability of the craniovertebral region, site of encroachment, and associated neural abnormalities.⁶ Since then, more than 6,000 pediatric and adult patients with various craniovertebral disorders have been evaluated at the hospitals and clinics of the University of Iowa. More than 1,900 of these bony abnormalities occurred in children younger than 16 years of age. This experience has helped define the natural history and the anatomical, biomechanical, and embryologic basis of craniovertebral pathology, and this knowledge in turn has led to an improved understanding and treatment of these complex disorders.

27.1 Relevant Anatomy and Biomechanics

The occipitoatlantoaxial complex is the most mobile and complex joint of the axial skeleton.² Flexion and extension occur at the occipitoatlantal and the atlantoaxial articulations (► Fig. 27.1a,b). In children, the anteroposterior translation between the anterior arch of atlas and dens, the “predental space,” can be up to 5 mm until the age of 8 years and should be less than 3 mm in adults.^{2,7,8} Cervical rotation occurs primarily at the atlantoaxial joint. Atlantoaxial rotation beyond 35 degrees is associated with a risk for contralateral vertebral artery injury.⁴ Further rotation exceeding 45 degrees is associated with facet interlock between the atlas and axis vertebrae (► Fig. 27.2 a–g). This has particular significance in atlas assimilation, for children participating in contact sports, and for those who undergo excessive rotation of the head during general anesthesia or forceful head manipulations. The absence of uncovertebral joints as well as the horizontal orientation of facets in children also raise the risk for upper cervical injury.

The cervical paraspinal musculature and ligamentous complex impart stability to the craniovertebral articulation and also form the pathogenic basis of various craniovertebral junction anomalies.^{2,9} The most critical craniovertebral ligament is the transverse ligament, which maintains mechanical stability of the atlantoaxial joint complex.¹⁰ It allows atlantoaxial rotation up to 47 degrees while preventing anterior subluxation of C1 on C2. The alar ligaments extend from the basion to the axis and serve to secondarily stabilize the C1–C2 joint and prevent extreme axial lateral rotation beyond 90 degrees.¹⁰ Alar ligamentous injury is typically associated with whiplash injuries. With disruption of the cruciate ligament, the load is then placed on the alar and the apical ligaments, which quickly become incompetent.⁷

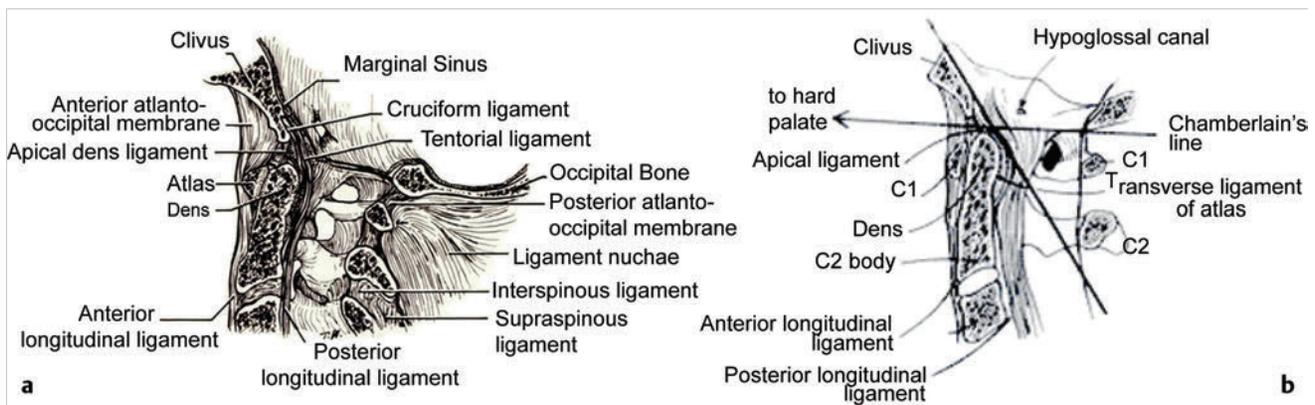


Fig. 27.1 (a) Craniocervical junction anatomy with ligaments and bursae present. (b) Line drawing depicting the cervicobasilar relationships.

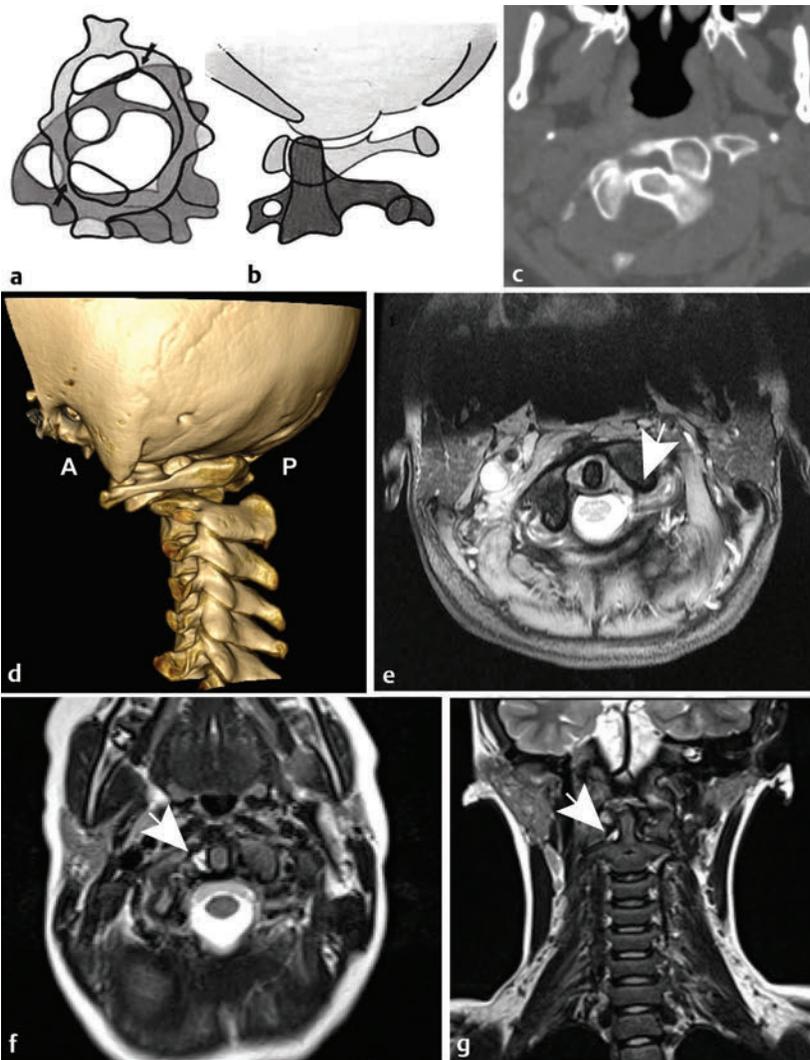


Fig. 27.2 (a,b) Rotational changes at atlantoaxial articulation as a result of rotation exceeding 40 degrees with an interlock (arrows). (c) Axial computed tomographic scan showing C1–C2 interlock. (d) Three-dimensional reconstructed image indicates the abnormal bony configuration. A, anterior; P, posterior. (e) Axial T2-weighted image indicates rotation of C1 on axis with a torn cruciate ligament (arrow). (f) Axial T2-weighted image in another patient indicates increased signal intensity within the alar ligament, adjacent to the odontoid (arrow). (g) Coronal T2-weighted image indicates the presence of a torn alar ligament (arrow) in the same patient.

Lymphatic drainage of the occipitoatlantoaxial joints is primarily through retropharyngeal nodes into the deep upper cervical lymphatic chain. These nodes also drain the nasopharynx, retropharyngeal area, and paranasal sinuses.^{2,11–14} Hence, a retrograde inflammatory change may affect the synovial lining of the craniocervical joint complex, with resultant effusion, instability, and subsequent possible neurologic deficit. This has been referred to as Grisel syndrome.¹¹ The atlantoaxial joints are the most vulnerable and affected in majority of patients. In addition, the periodontal venous plexus and suboccipital epidural sinuses communicate with the pharyngovertebral veins. This can result in osteomyelitis of the craniocervical joints due to paravertebral infections.¹³

The vertebral and the occipital arteries provide blood supply to the craniocervical region.¹³ The vertebral arteries give rise to anterior and posterior ascending branches that anastomose in an apical arcade and supply small perforating branches to the axis body and odontoid process.¹⁵ In addition, ascending anterior branches receive contributions from the carotid arteries. The cartilaginous plate between the dens and axis body prevents the development of a vascular communication between the axis

and its odontoid process. This accounts for formation of a sequestrum in type 2 odontoid fractures and the development of os odontoideum.² Cervicomedullary pathology may also present with false localizing symptoms due to medullary decussation at the foramen magnum and secondary involvement of the lower cervical cord segments due to venous stasis resulting from extramedullary compression of the cervicomedullary junction.⁵

27.2 Classification of Craniovertebral Junction Abnormalities

Craniovertebral anomalies are typically developmental disorders of the cartilaginous neurocranium and adjacent vertebral skeleton.¹⁶ In addition, a wide variety of congenital, hereditary, and acquired anomalies may exist either individually or in combination (see box “Classification of Craniovertebral Anomalies (p.344)”).

Classification of Craniovertebral Anomalies

- Congenital anomalies and malformations
 - Occipital sclerotome malformations: proatlas remnants, clavus segmentations, condylar hypoplasia, atlas assimilation
 - Atlas malformations: bifid atlas, assimilation, fusions, absent arches
 - Axis malformations: segmentation defects, odontoid dysplasias
- Developmental and acquired abnormalities
 - Foramen magnum abnormalities
 - Foramen stenosis: achondroplasia
 - Secondary invagination: osteogenesis imperfecta, Hadju-Cheney syndrome, renal rickets, Paget disease
 - Atlantoaxial instability
 - Down syndrome
 - Errors of metabolism: Morquio syndrome, Hurler syndrome
 - Infections: Grisel syndrome, tuberculosis
 - Trauma
 - Inflammation: regional ileitis, juvenile rheumatoid arthritis, Reiter syndrome
 - Tumors: osteoblastoma, eosinophilic granuloma, chordoma, neurofibromatosis
 - Miscellaneous: Conradi syndrome, fetal warfarin, syringomyelia

Signs and Symptoms of Craniovertebral Anomalies: Insidious or Rapid Onset of Symptoms and Signs

- Head tilt
- Short neck, low hairline, limitation of neck motion
- Web neck
- Scoliosis
- Features of skeletal dysplasias
- Neck pain and posterior occipital headache
- Basilar migraine
- Hand or foot isolated weakness
- Quadriparesis/paraparesis/monoparesis
- Sensory abnormalities
- Nystagmus, usually downbeat and lateral gaze
- Sleep apnea
- Repeated episodes of aspiration pneumonia, dysphagia
- Tinnitus and hearing loss
- Vertigo

27.3 Epidemiology

Underlying craniovertebral anomalies must be suspected in infants with skeletal dysplasias and syndromic disorders like Goldenhar syndrome and Conradi syndrome.^{17–20} Children with Down syndrome have a 14 to 20% incidence of atlantoaxial instability.^{2,21} In Morquio syndrome, a combination of atlantoaxial instability, C2–C3 segmentation failure, os odontoideum, and cervicothoracic abnormalities occurs in 30 to 50% of patients.^{2,21} With an underlying congenital craniocervical anomaly, secondary developmental and acquired phenomena may supervene, producing basilar invagination.²²

27.4 Signs and Symptoms

Craniovertebral disorders present with a constellation of symptoms and signs that reflect dysfunction of the brainstem, cerebellum, cervical spinal cord, cranial nerves, cervical roots, and their associated vascular supply (see box “Signs and Symptoms of Craniovertebral Anomalies: Insidious or Rapid Onset of Symptoms and Signs (p.344)”). The onset may be insidious or rapid, and at times patients may present with false localizing signs. Infrequently, a rapid neurologic progression is followed by sudden death. More commonly, an antecedent history of trauma triggers symptoms that may progress rapidly. The authors feel strongly that children with nasopharyngeal infections and neck spasm (“torticollis”) must be suspected of harboring craniocervical instability unless it is proven otherwise. Temporary bracing and close follow-up with flexion–extension X-rays repeated on a weekly basis will aid in the identification of any underlying instability that can sometimes be masked by muscular spasm in acute presentations.

An abnormal general physical appearance is often seen in children with congenital craniocervical abnormalities. The head may be tilted or cocked to one side in patients with atlantoaxial rotary subluxation or partial segmentation failure. The classic triad of the Klippel-Feil syndrome consists of an abnormally low hairline posteriorly, a short neck, and limitation of neck movement, which may present in conjunction with facial asymmetry and neck webbing.²³ Scoliosis is often present. An abnormal stature and elevated scapula are seen with Sprengel deformity. Systemic skeletal anomalies are typically present, with craniovertebral abnormalities secondary to spondyloepiphyseal dysplasia, achondroplasia, and other types of dwarfism.^{19,24}

Cervical and occipital pain occurs in up to 85% of children and is described as originating in the suboccipital region with radiation to the vertex.^{2,5} “Basilar migraine” occurs in 25% of children affected with basilar invagination and medullary compression and is due to associated compression of the vertebral basilar vessels. Occipitoatlantoaxial instability may cause repeated trauma to the anterior spinal artery and the perforating vessels of upper cervical cord and medulla, leading to vascular spasm or occlusion and secondary neurologic deficits.

The most common neurologic deficit encountered in the 1,700 children in our series was myelopathy. This was equally distributed with motor deficits involving monoparesis, hemiparesis, paraparesis, and quadriparesis. Myelopathy mimicking the “central cord syndrome” was frequently encountered in children with basilar invagination. Similarly, posterior column dysfunction was the most common sensory abnormality. Occasionally, children described an abnormal sensation in their hands or feet. In infants and toddlers, this may be recognized by constant rubbing of the affected limbs. Brainstem and cranial nerve deficits are usually evident by dysphagia and repeated episodes of aspiration pneumonia and sleep apnea. Not uncommonly, internuclear ophthalmoplegia is present, leading to a misdiagnosis of mesencephalic and upper pontine disturbance. Downbeat nystagmus was present more often in patients with an associated Chiari 1 malformation. Unilateral or bilateral paralysis or dysfunction of the soft palate and pharynx leads to repeated bouts of aspiration pneumonia as well as poor feeding

and inability to gain weight. The most common cranial nerve dysfunction was hearing loss in 23% of children and is most commonly associated with Klippel-Feil syndrome. Vascular symptoms, such as intermittent attacks of altered consciousness, transient visual loss, vertigo, and confusion, occurred in 20% of children. At times, this was provoked by cervical extension or rotation or by manipulation of the head and neck.

27.5 Imaging

Plain radiographs of the cervical spine in lateral and anteroposterior views are supplemented by open-mouth and anteroposterior projection views of the foramen magnum.⁸ If instability is suspected, lateral extension and flexion views should be obtained.^{2,5} Several lines of reference have been described to correlate the position of neural structures with the associated osseous abnormality (► Fig. 27.1b).^{3,8} The Chamberlain palato-occipital line joins the hard palate to the posterior edge of the foramen magnum. In a normal individual, the tip of the dens should lie below this line or at most 3 to 5 mm above it.³ When the odontoid process ascends above this line, basilar invagination has occurred. We believe that the Wackenheim clivus-canal line (drawn along the clivus and extrapolated into the cervical spinal canal) is of great significance. The odontoid process must be ventral or tangential to this line under normal conditions, and it transects this line in basilar invagination, atlantoaxial dislocation, and anterior occipitoatlantal dislocation. The McRae foramen magnum line joins the anterior and posterior edges of the foramen magnum, and the tips of the dens must be below this line.¹ A sagittal diameter of less than 20 mm at the cervicomedullary junction is associated with neurologic compromise.²²

Magnetic resonance (MR) imaging aids in an ideal identification of the underlying neural abnormalities and associated osseous compression.^{8,24} Computed tomography (CT) with rapid-acquisition spiral technique and three-dimensional reconstruction is necessary to recognize the presence or absence of epiphyseal growth plates, the extent of fusion, segmentation defects, and “missing” osseous components, especially in infants with torticollis.⁸ In all the techniques of investigation, dynamic flexion–extension studies are necessary for assessing stability and the angular osseous relationships with underlying neural structures (► Fig. 27.3). This also provides information regarding reducibility and the optimal position of fixation if needed.^{2,5} Because of their routine availability, MR imaging and CT angiography have supplanted traditional angiography to identify obstruction or potential occlusion with dynamic positional changes.²

27.6 Surgery

Factors that influence specific treatment are the following: (1) the etiology of the pathologic process (i.e., type of bony abnormality and the presence of Chiari malformation, syrinx, or vascular abnormalities); (2) the reducibility of the bony lesion (ability to restore normal anatomical alignment and relieve compression of the cervicomedullary junction); (3) the mechanics of compression and direction of encroachment; and (4) the presence of abnormal ossification centers and epiphyseal

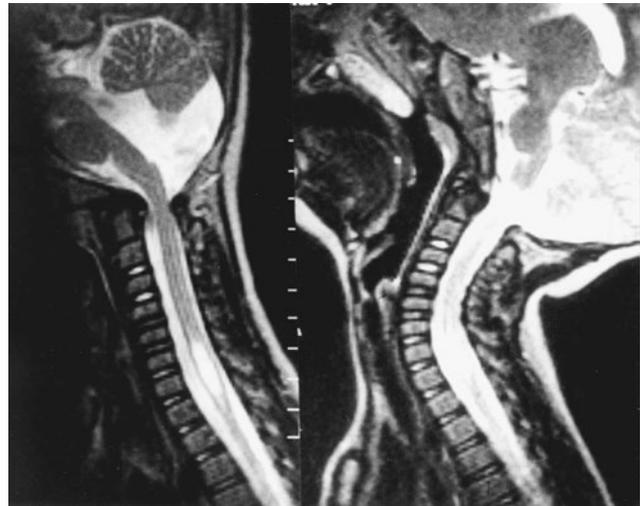


Fig. 27.3 Composite of magnetic resonance imaging of the craniocervical junction in the T2 mode. The flexed position is seen on the left and the extended position on the right. Note the instability at the craniocervical junction. A syrinx is seen in the lower cervical spinal cord.

growth plates.^{2,6} The primary goal underlying surgical treatment is to relieve compression at the craniocervical junction (► Fig. 27.4a–c). In a reducible lesion, stabilization is paramount to maintain neural decompression. Irreducible lesions require decompression at the encroachment site. Ventral lesions require operative approaches through a transpalatopharyngeal decompression, a Le Fort drop-down maxillotomy, or the lateral extrapharyngeal route. Posterior or posterolateral decompression is required for dorsal lesions (► Fig. 27.5). If instability is present after decompression, a posterior fixation is mandatory for stability (► Fig. 27.6a–d).

The management of craniocervical instability in young infants secondary to conditions such as Goldenhar syndrome and osteogenesis imperfecta deserves special mention.² It is essential to determine the potential for osseous development by identifying developing epiphyseal growth plates on thin-section CT. In these instances, we use custom-built cervical orthoses to impart occipitocervical stability while skeletal growth is allowed to occur. During follow-up, the cervical orthoses are replaced periodically and diagnostic studies repeated to monitor the craniocervical region. After adequate bone growth is achieved by 3 to 4 years of age, surgery is undertaken, as described above, if osseous stability has not yet occurred.

Skeletal traction is applied with an MR imaging-compatible crown halo device.^{25,26} In children between 2 and 4 years of age, eight-point fixation is utilized with finger pressure that limits pin pressure to 1 to 1.5 lb of torque. At 5 years of age, 4 lb of maximum pin pressure is utilized. Traction is initiated at 3 to 4 lb and does not exceed 7 lb. Reducible lesions that are the result of inflammatory states or recent trauma will respond to conservative treatment with external immobilization once reduction is achieved. If this does not occur or if the condition is not the result of trauma or infection, surgical fixation is mandated. In children, traction is applied in the operating room under general anesthesia. A cervical collar is used for protection

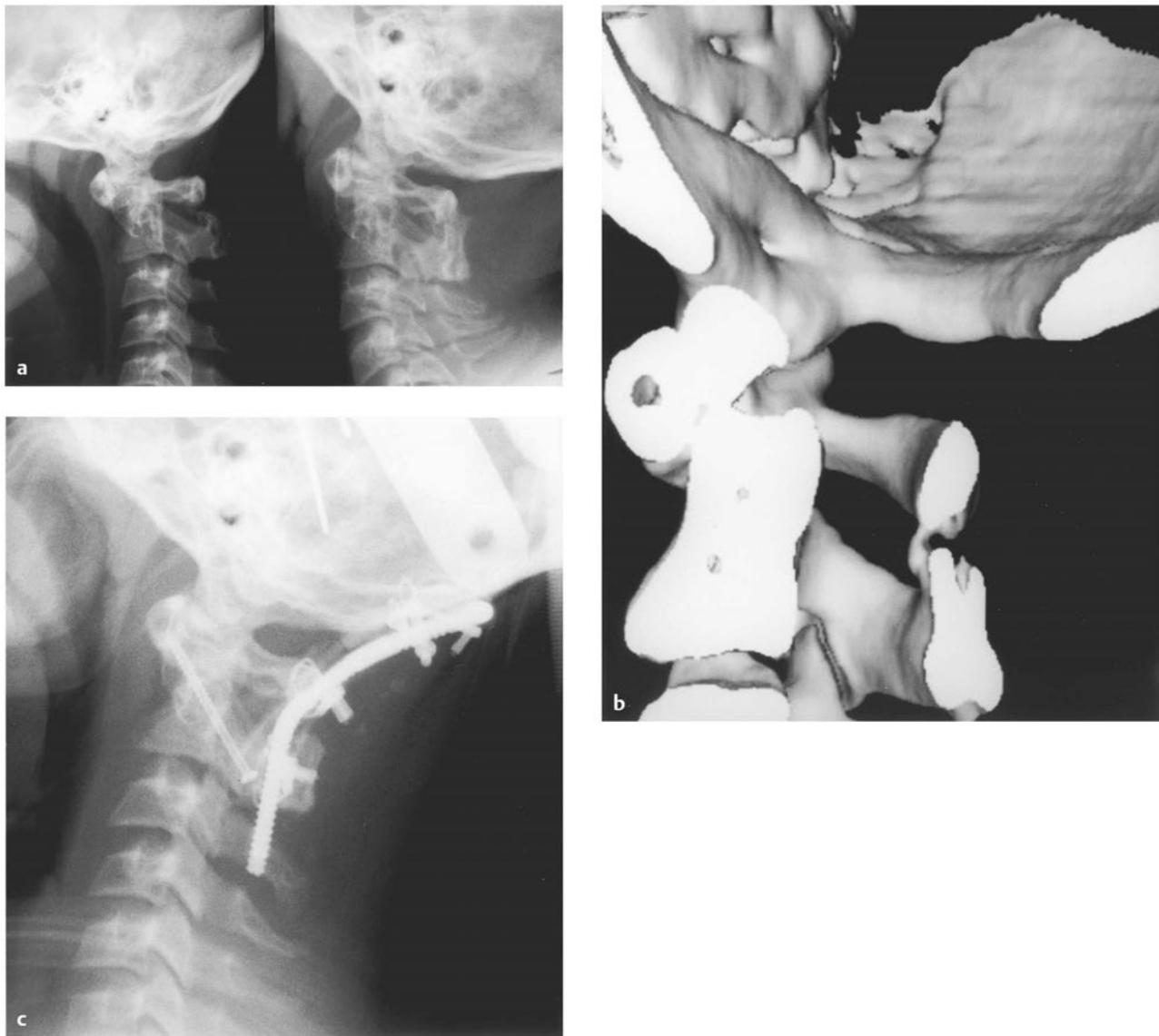


Fig. 27.4 (a) Composite of a lateral craniocervical radiograph in the flexed (left) and extended (right) position in an 11-year-old child with Down syndrome. A previous attempt at dorsal atlantoaxial arthrodesis failed. Instability and an os odontoideum are present. (b) Three-dimensional computed tomography of the craniocervical junction demonstrates the failed dorsal interspinous fusion between C1 and C2. An os odontoideum is present. (c) Postoperative lateral cervical spine and craniocervical radiograph. The halo vest is in place. A dorsal occipitoatlantoaxial arthrodesis is made with titanium loop instrumentation and a rib graft. Because of the gross instability at the occipitoatlantoaxial articulation, a transarticular screw between C2 and C1 completed the stabilization.

during intubation maneuvers. After the initial use of general mask anesthesia, fiber-optic intubation is undertaken through the mask. Halo ring traction is then applied during pharmacologic muscle relaxation with general anesthesia. Neurophysiologic monitoring (somatosensory evoked potentials) is maintained during these maneuvers, in addition to image documentation with intraoperative computed tomography with three-dimensional display.²⁷ This is a recent technique developed in the last 4 years. Basilar invagination, craniocervical junction dislocation, and other irreducible states warrant this attempt at “reduction.” It has proved successful in 36 of 52 patients whose abnormalities were felt to be “irreducible.” These patients will not require ventral decompression, but posterior

decompression and stabilization. If surgical fixation is planned simultaneously, an interim clinical assessment is made after reversal of anesthesia while intubation is maintained.

In the case of a grossly unstable but reducible state, a crown halo vest is placed under general anesthesia, and the child is then turned prone on the operating table. The posterior struts are removed to enable dorsal fixation while the ventral struts are maintained for immobilization and to aid postoperative re-application of the halo vest.

In addition to the traditional transoral transpharyngeal surgical approaches, transnasal and transcervical endoscopic techniques have evolved to establish surgical access for the management of irreducible ventral craniocervical lesions.^{28,29} The

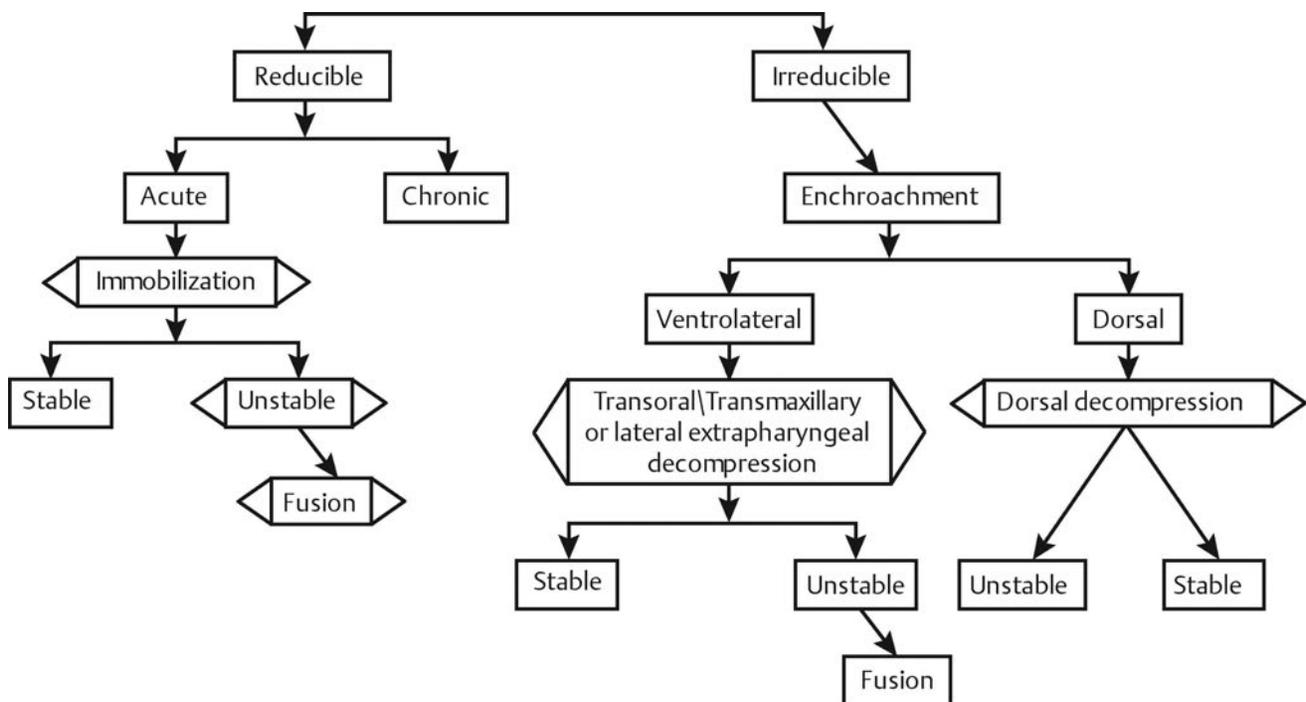


Fig. 27.5 The treatment of craniovertebral abnormalities.

transoral transpharyngeal route offers excellent surgical exposure to address a wide range of ventral craniovertebral junction lesions,³⁰ but it is associated with the surgical morbidity of postoperative dysphagia and the need for postoperative intubation after surgical dissection through the palate and pharynx. The endonasal approach enables access to the rostral craniocervical junction, and it avoids prolonged postoperative intubation and the risk for oropharyngeal dysfunction associated with transoral procedures. Conversely, the surgical access corridor is restricted in the lateral and inferior limits of the exposure, and endoscopic pharyngeal closure is not made. The endoscopic transcervical route circumvents the need for oropharyngeal dissection, and it offers a sterile operative field while enabling adequate exposure.²⁹ Spinal deformity, obesity, or ventral chest wall constraints, however, limit its application. It is also associated with a risk for airway swelling and dysphagia. An endoscopic transoral approach has also been proposed that obviates the need for resection through the hard palate while improving surgical access and endoscopic visualization.³¹ Although these evolving techniques may potentially improve patient outcomes, long-term studies with a direct comparison of outcomes are needed to better address the role of these emerging techniques.

Atlantoaxial osseous fusion requires immobilization for at least 3 months. We utilize custom brace/vest immobilization for 5 to 6 months when only a bony fusion is made. The rate of failure of fusion reaches 50% when immobilization is inadequate. Dorsal wire fixation should be avoided because skeletal growth will cause stress fatigue, with resultant wire fracture or disruption and possible injury to spinal cord.^{2,32,33} In the management of pediatric craniocervical fusions, the age of the patient, the occipitoatlantoaxial dimensions, and the ability to achieve screw purchase for an instrumented fusion must be taken into consideration. The senior author (A.H.M)

has used full-thickness rib to span the dorsal structures in children younger than 5 to 6 years of age; an attempt at instrumentation is made in children past that age.^{25,34} The treatment guidelines outlined above have yielded excellent surgical results, with no mortality or gross morbidity, in more than 1,700 children treated via anterior, lateral, or posterior surgical routes.

27.7 Specific Conditions Affecting Children

27.7.1 Grisel Syndrome

Grisel syndrome is defined as spontaneous atlantoaxial subluxation following parapharyngeal infection.^{2,11–13,15} This inflammatory subluxation is attributed to metastatic inflammation causing ligamentous stretching, subluxation, muscle spasm, and regional hyperemia with decalcification of ligamentous attachments. Thus, these children may present with torticollis, stiff neck with neck pain, or neurologic deficit. This may be after a case of tonsillitis, mastoiditis, retropharyngeal abscess, or otitis media or after a surgical procedure to correct one of these states. Children younger than 12 years of age are most commonly affected because of their relative ligamentous laxity and atlas vascularity.

Treatment involves CT and MR imaging. These identify the underlying abnormal anatomy and infection. It is critical that the source of infection be eliminated. Stabilization is achieved with a sterno-occipital mandibular immobilizing brace or a halo vest. In the acute phase, a Philadelphia collar may be applied to allow careful monitoring of respiratory function. Once the infection is under control, it is important that the

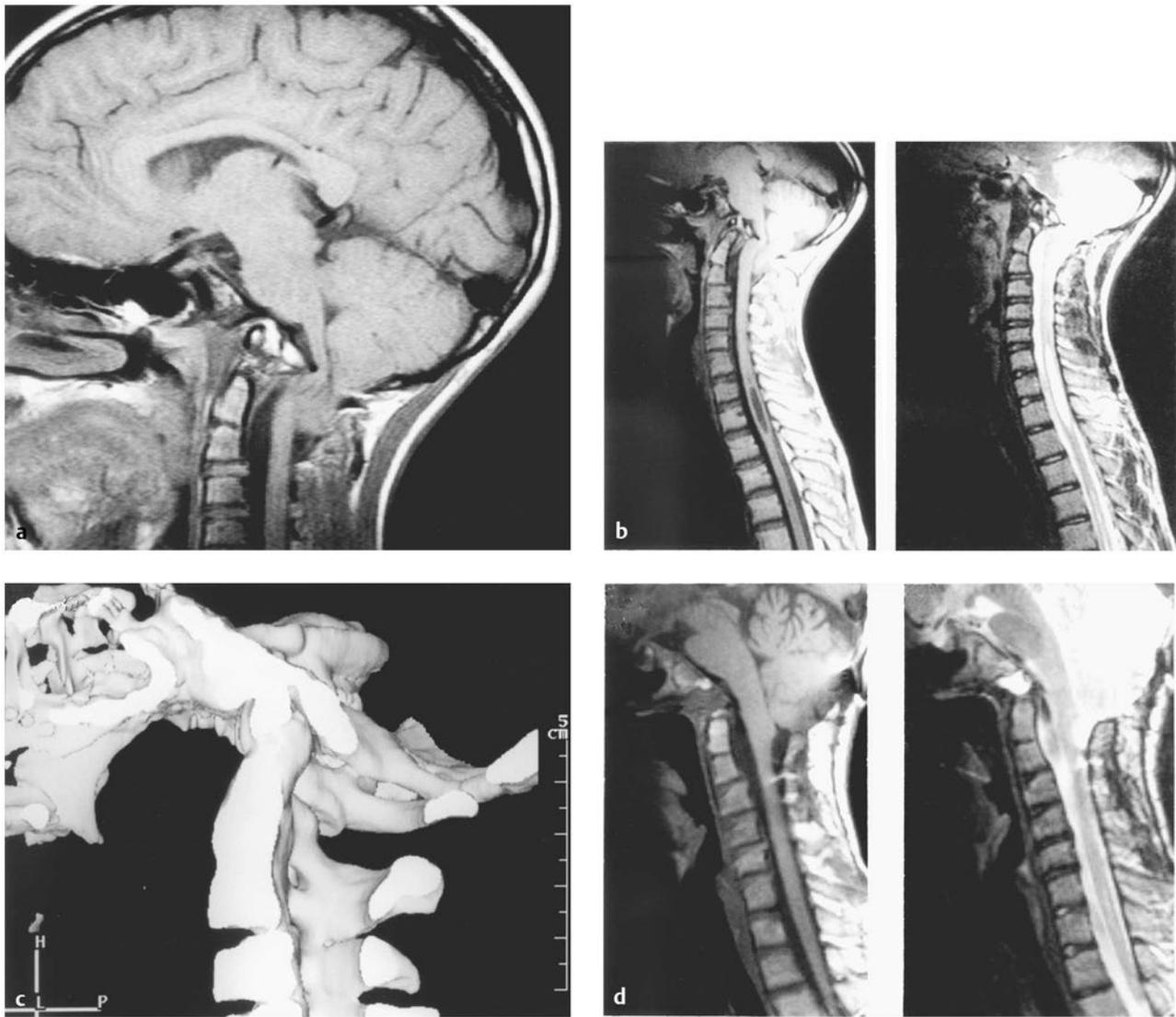


Fig. 27.6 (a) Lateral magnetic resonance (MR) imaging in T1 mode in a 12-year-old girl with palsies of cranial nerves IX, X, and XII bilaterally. There is a ventral indentation into the inferior medulla by a bony mass proceeding from the inferior clivus. A hindbrain herniation is visualized. (b) MR imaging in T1 (left) and T2 (right) mode shows the ventral medullary and basilar artery compression. A hindbrain herniation and a cervicothoracic syrinx are visualized. (c) Three-dimensional computed tomography of the craniocervical junction viewed from within. A proatlantal segmentation defect is seen. A protrusion from the inferior clivus extends into the ventral foramen magnum. There is basilar invagination present and atlas assimilation laterally. (d) Postoperative MR imaging in T1 (left) and T2 (right) mode visualizing the posterior fossa and cervical spine. The patient underwent a transpalatopharyngeal resection of the inferior clivus, proatlantal segmentation bony abnormality, and odontoid process. Note the decompression and absence of the syrinx.

craniocervical dynamics be carefully assessed. In the author's own series of 52 children, a fusion procedure was required in 2 patients.² A delayed diagnosis of torticollis and ligamentous instability following an upper respiratory infection in infants often confounds effective treatment.

27.7.2 Assimilation of the Atlas and the Klippel-Feil Syndrome

Atlas assimilation is defined as segmentation failure between the fourth occipital and first spinal sclerotome. This occurs in

0.25% of the population; it may be unilateral, bilateral, segmental, or focal and in most instances occurs in conjunction with other abnormalities. Atlas assimilation was present in 380 of 3,300 patients with craniocervical abnormalities evaluated in an initial series of the senior author.²² A Chiari 1 malformation is typically present in more than one-third of such individuals.³⁵ Associated segmentation failure of the second and third cervical vertebrae leads to atlantoaxial instability that often progresses to a reducible basilar invagination (► Fig. 27.7a–d). This is more common in children younger than 14 years of age, after which irreducible basilar invagination occurs. During the phase of reducibility, prolific granulation tissue crowning the

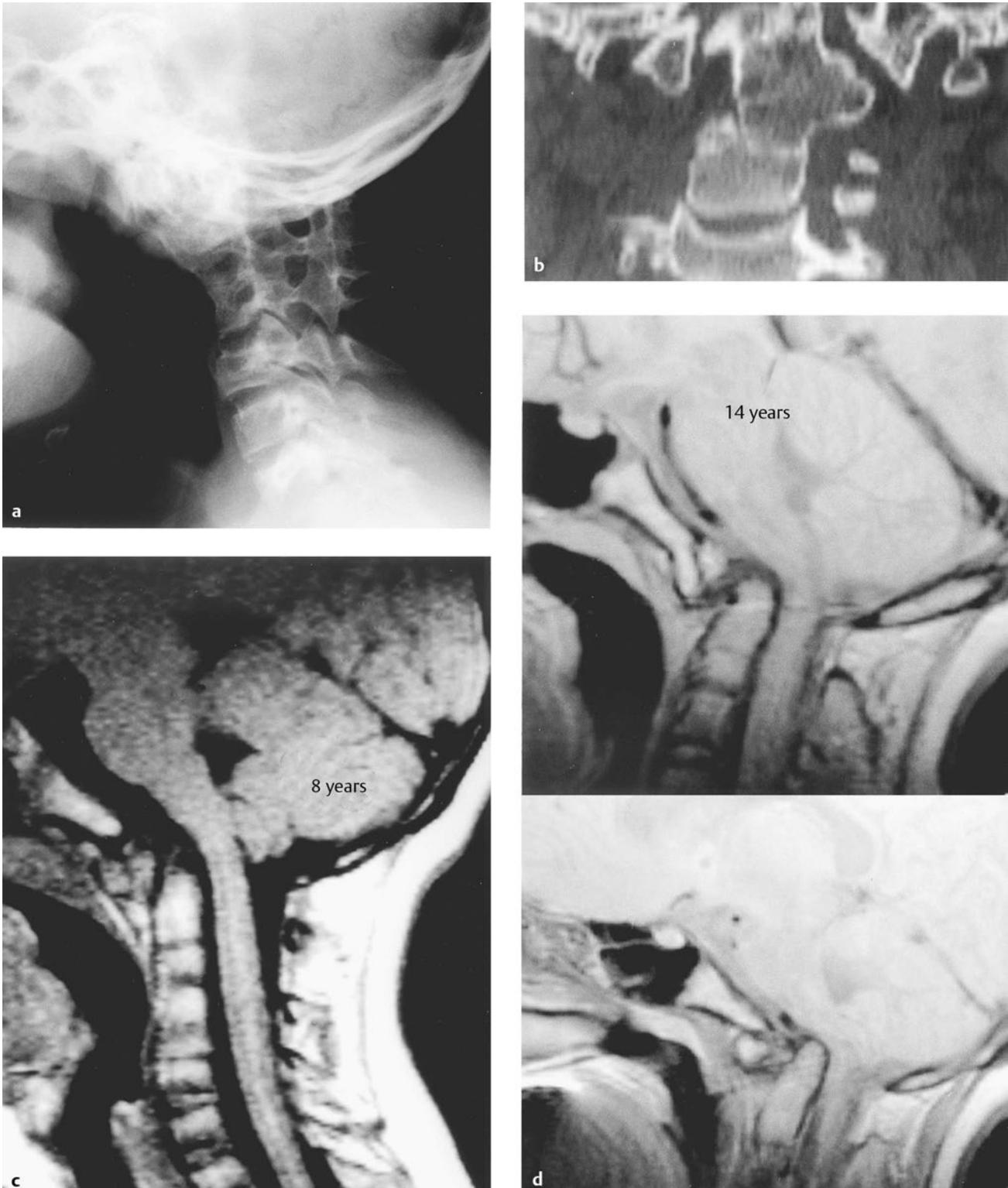


Fig. 27.7 (a) Lateral cervical spine and skull radiograph in a 14-year-old with neck pain following a football incident. The patient presented with weakness in the upper limbs and a diminished gag reflex with mirror hand movements. Note the segmentation failure at C2 and C3. (b) Frontal two-dimensional computed tomographic reconstruction of the craniocervical region identifies atlas assimilation and an abnormal position of the odontoid process in a 14-year-old. (c) This child had previously undergone magnetic resonance (MR) imaging for neck pain at 8 years of age. There is a mild atlantoaxial dislocation with probable atlas assimilation. However, the cervicomedullary junction is not compressed. (d) Composite of T2-weighted MR imaging in the midline (left) and paramedian (right) locations. The MR imaging at the age of 14 years now shows gross atlantoaxial dislocation with basilar invagination of the odontoid process into the foramen magnum, compressing the inferior medulla.

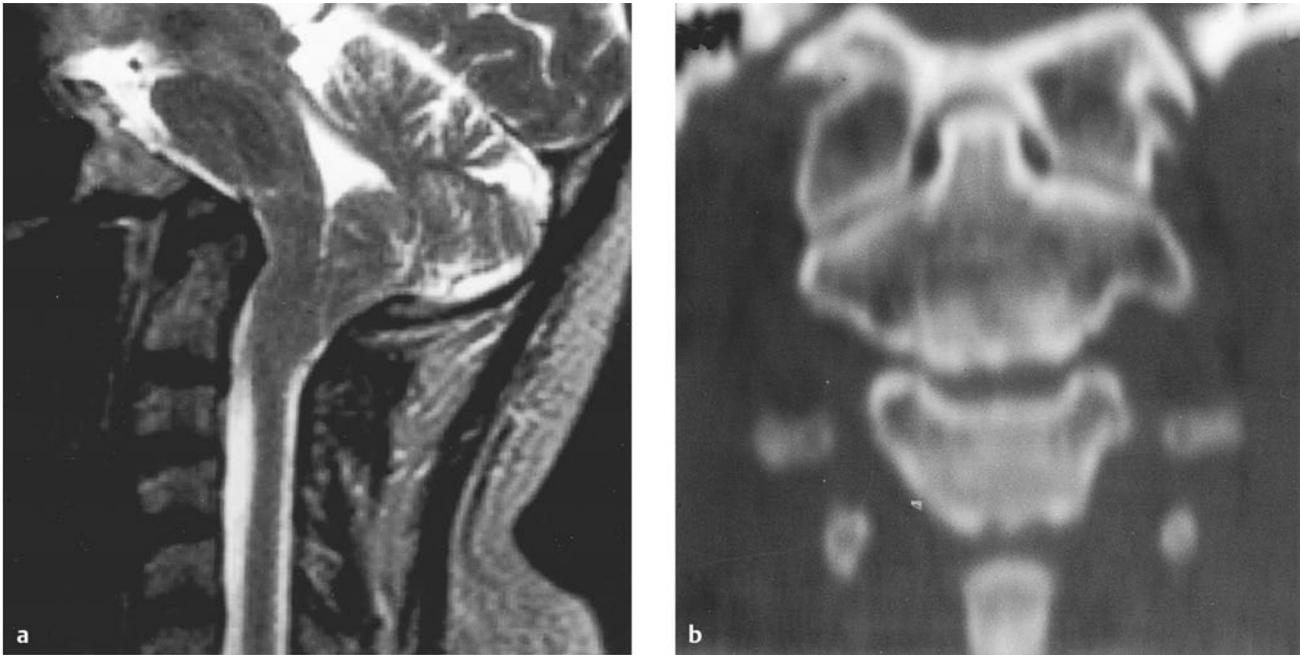


Fig. 27.8 (a) Midsagittal T2-weighted magnetic resonance imaging of the craniocervical region. This demonstrates a hypoplastic basiocciput, with the clivus nearly horizontal. There is atlas assimilation, with the anterior arch of the atlas located between the inferior clivus and the odontoid process. The vertical height of the posterior fossa is grossly reduced. The clivus-odontoid articulation indents into the mid medulla. Hindbrain herniation is visualized. (b) Coronal computed tomography through the plane of the odontoid process reveals atlas assimilation and abnormal craniocervical relationships.

odontoid process aggravates cervicomedullary compression. In irreducible basilar invagination, an associated horizontally oriented clivus and abnormal grooving occur behind the occipital condyles as a result of upward migration of the axis vertebra onto the assimilated atlas, leading to irreducibility (► Fig. 27.8a, b). Hence, atlantoaxial dislocation or basilar invagination is more likely to be reducible in children younger than 16 years. This is especially pertinent in the surgical management of hindbrain herniation syndromes because posterior decompression alone does not address the underlying craniocervical instability.

Acute trauma (e.g., flexion-extension injuries) and chronic trauma (e.g., from carrying loads on the head, as in developing countries) have been implicated in precipitating symptoms of atlantoaxial instability. This is more common when atlas assimilation is present in combination with segmentation failure of the second and third cervical vertebrae. Unilateral atlas assimilation may present as torticollis in a young child. It is essential that these anomalies be recognized during operative positioning involving excessive head rotation.

The classic triad of Klippel-Feil syndrome includes a short neck, a low posterior hairline, and limitation of cervical motion. This syndrome is commonly associated with atlas assimilation, fused vertebrae, segmentation anomalies, and spina bifida occulta. Scoliosis has been identified in 50% of reported cases.² Commonly associated congenital abnormalities include facial developmental anomalies (cleft face, deafness, high-arched palate, and facial palsies) and cardiovascular abnormalities (mitral valve disease, ventricular septal defects, aortic coarctation, and patent ductus arteriosus). Thoracic anomalies, including skeletal dysplasia, ectopic lung, and rib fusions, can occur in up to

20% of individuals. Genitourinary tract anomalies, including unilateral kidney, horseshoe kidney, and ectopic kidneys, occur in up to 30% of individuals. Hearing loss is generally of a mixed conductive and sensorineural type and may occur in 18% of children. It is imperative that these abnormalities be diagnosed and addressed perioperatively.¹

27.7.3 Atlantoaxial Rotatory Subluxation

The biomechanical properties of the pediatric craniovertebral junction, described earlier, predispose children to the development of atlantoaxial rotatory subluxation, which may also arise in conjunction with congenital (Down syndrome, Morquio syndrome) and acquired (trauma, preceding nasopharyngeal infections, Grisel syndrome) conditions.^{9,36,37} Symptoms commonly include cervical pain, limitation in cervical rotation, and torticollis that often leads to the characteristic “cock robin” position, in which rotation of the head and neck toward opposite sides is combined with cervical flexion (► Fig. 27.2d).^{37,38}

Upon presentation, the work-up includes a detailed clinical history with documentation of any preceding trauma, infectious or inflammatory conditions, and additional symptoms associated with an underlying congenital condition. An accurate determination of symptom onset is critical because this dictates whether a conservative or an operative management plan is appropriate. Clinical examination helps differentiate atlantoaxial rotatory subluxation from torticollis.³⁸ A thin-cut CT examination of the cervical spine with three-dimensional reconstruction helps identify the abnormal locked configuration of the

C1–C2 facet joints and also aids in preoperative planning (► Fig. 27.2a–d). A dynamic CT examination with the head in neutral and lateral rotation toward each side has also been recommended to document the limitation or loss of motion between the C1 and C2 levels during lateral rotation that is considered diagnostic. MR imaging is essential to evaluate ligamentous disruption, although in some chronic cases, radiographic changes may not be evident because of long-standing ligamentous laxity (► Fig. 27.2e,f).

Treatment entails cervical realignment with immobilization. In patients without a preceding infection, an initial trial of external bracing, with appropriate antibiotics and muscle relaxants, is undertaken. Otherwise, cervical traction (refer to earlier section on surgery) with the concurrent use of muscle relaxants, is needed to restore cervical anatomical alignment. For children with an acute presentation and a symptom duration of less than 2 weeks, an external cervical orthosis, with close clinical and radiographic follow-up, may suffice to maintain realignment and establish immobilization for healing.^{37,38} For those with a subacute presentation, symptom recurrence, or repeated subluxation, closed reduction with a cervical halter or halo traction is advocated, preferably in an inpatient setting.³⁸ If cervical alignment is reestablished, then an external orthosis should be continued for at least 3 months. For those with chronic or refractory symptoms or recurrent atlantoaxial rotatory subluxation, operative fixation with occipital-cervical arthrodesis is advocated because the ligamentous complex may be irreversibly damaged. Left untreated, atlantoaxial rotatory subluxation often leads to chronic pain, rotational deformity, and pharyngeal compression.³⁸ Moreover, a delayed diagnosis is often responsible for the failure of conservative treatment and increases the risk for recurrence.³⁷

27.7.4 Basilar Invagination

Basilar invagination implies ascent of the vertebral column through skull base.² It is a primary developmental defect and is usually associated with block vertebrae, fusion defects, and occipitalization of the atlas vertebra. If unilateral condylar hyperplasia occurs, this often leads to torticollis. The common manifestations of dysgenesis are the Chiari 1 malformation and syringohydromyelia, which occurs in 35% of patients. The terms *basilar invagination*, *basilar impression*, and *platybasia* require clarification. Basilar invagination implies the primary form, consisting of a distinct developmental defect of the chondrocranium. Basilar impression refers to the secondary, acquired form of invagination that is due to the bone softening that occurs in rickets, hyperparathyroidism, osteomalacia, Paget disease, Hurler syndrome, and other diseases, such as Hadju-Cheney syndrome.^{2,5} Platybasia refers only to an abnormally obtuse basilar angle formed by joining the plane of the clivus with the plane of the anterior fossa of the skull. This angle is of anthropologic significance only. There are no symptoms or signs that can be attributed to platybasia alone. It is not a measure of basilar invagination, although it may be associated with invagination.

Basilar invagination implies involvement of the basioccipital, exoccipital, and squamous occipital bone and is of two types. In anterior or ventral basilar invagination, the basiocciput is shortened and the clivus is small and may be horizontally oriented, leading to rostral displacement of the foramen magnum. This is

often associated with platybasia and hindbrain herniation syndromes. The paramedian type of basilar invagination involves hypoplasia of the occipital condyles with dorsal displacement of the clivus into the posterior fossa. The clivus invagination is compensated for by an excessive downward curving of the lateral portion of the squamous occipital bone.

Basilar invagination should be suspected when the lateral atlantoaxial articulation cannot be visualized on the open-mouth projection radiograph. A definitive radiographic diagnosis involves verifying the pathologic alteration in the relationships of affected bone and neural structures on radiographs and on CT and MR imaging studies (► Fig. 27.8a,b). In our series, neurologic deficit was usually present in patients older than 8 years of age if the effective sagittal diameter (subarachnoid) of the foramen magnum was less than 19 mm.

Cervical traction should be applied with an MR imaging-compatible crown halo. In the event of an associated Chiari malformation, ventral cervicomedullary bony decompression is performed in cases of irreducible invagination before the posterior surgical procedure. Failure to do so results in lack of neurologic improvement or progression of neurologic deficit. The ability to reduce the invagination is age-related, as previously described for atlas assimilation.²² If present, syringohydromyelia is effectively managed by proceeding with ventral decompression first. This enables restoration of the craniospinal cerebrospinal fluid (CSF) dynamics and resolution of the syringohydromyelia.³⁹ Any associated hydrocephalus should be treated by ventriculoperitoneal shunting. Endoscopic third ventriculostomy is not recommended, given the abnormal anatomy of the basiocciput and high-riding basilar artery.

27.7.5 Basilar Impression and Bone Softening Syndromes

Basilar impression, or secondary basilar invagination, arises secondary to congenital (osteogenesis imperfecta, spondyloepiphyseal dysplasia, acro-osteolysis, Hurler syndrome, achondroplasia) or acquired (Paget disease, osteomalacia, hyperparathyroidism, renal rickets) skeletal metabolic disorders.^{20,40,41} Anatomically, there is infolding of the squamous occipital bone, leading to elevation of the posterior fossa floor with invagination of the foramen magnum margin.²⁰ The basiocciput is also elevated and foreshortened, with associated truncation and relative horizontal orientation of the clivus that leads to an acute craniocervical angle. Anteroposteriorly, the petrous temporal bone is also deformed. These changes ultimately permit the clivus–atlas–odontoid complex to assume an abnormally rostral location within the foramen magnum, further restricting the posterior fossa volume.

The rostral extent of the invagination dictates the attendant neurologic manifestations (► Fig. 27.9a,b). The brainstem is elevated and splayed over the ventrally situated clivus–atlas–odontoid complex. In addition to causing mechanical compression, this acts as a fulcrum by which traction is applied to the caudal brainstem and rostral cervical spinal cord, producing bulbar dysfunction and myelopathy. The lower cranial nerves are stretched and distorted as the brainstem is forced upward, resulting in characteristic cranial nerve palsies. Cerebellar involvement may be primary, caused by compression from the



Fig. 27.9 (a) Lateral midsagittal magnetic resonance (MR) imaging (T1-weighted) of the head and upper cervical spine in a 7-year-old with basilar impression secondary to osteogenesis imperfecta. There is a horizontal clivus. The upper cervical spine is within the foramen magnum. This angulation causes a 90-degree indentation into the pontomedullary junction. There is secondary aqueductal stenosis with hydrocephalus. The vertical height of the posterior fossa is markedly reduced. Cerebellar tonsillar herniation is seen down to the C3 level. (b) Composite of T2-weighted axial MR imaging through the plane of the clivus (left) and 1 cm rostral to the dorsum sellae (right). There is upward invagination of the petrous bone and the atlas and axis seen on the left. The basilar artery is horizontal in its orientation at the level of the pontomesencephalic junction.

foramen magnum infolding, or secondary, caused by hindbrain herniation. Neurologic dysfunction may thus be coupled with hydrocephalus, syringohydromyelia, and hindbrain herniation. This acquired form of hindbrain herniation may lead to syringohydromyelia.

The pathogenesis of secondary invagination and osteochondroplasia remains obscure. The intrinsic bone fragility of the chondrocranium leads to deformation of both the skull base and cranial vault due to ineffective load bearing. Recurrent pathologic microfractures and chronic bone remodeling, evidenced by abnormal calluslike bony proliferation seen intraoperatively and also on radioactive imaging studies, may further contribute to bony deformation.²⁰

In pediatric patients with basilar impression or upper cervical abnormalities, the author has recommended a customized Minerva orthosis to “shore up” the skull and prevent the progression of secondary invagination.^{20,42} If a neurologic deficit has occurred secondary to ventral compression, a transoral or transmaxillary decompression, followed immediately by dorsal occipitocervical fixation with occipitocervical instrumentation and autologous bone grafting, must be undertaken. Postoperatively, occipitocervical immobilization must be continued through a modified shell custom-built brace until skeletal maturity is achieved. If any hydrocephalus due to secondary aqueductal stenosis is present, it must be treated first.

Surgical intervention was well tolerated in the author’s series, with a 100% fusion rate, effective neural decompression, and symptom improvement. However, although functional improvement persisted, basilar invagination progressed in 80% of the patients despite successful fusion.²⁰ In all these patients, the entire fusion mass migrated rostrally as a result of further squamous occipital and petrous bone infolding. Additionally, the posterior fusion mass tends to act as a fulcrum on which the

lever arm of the anterior skull base turns, thus exacerbating ventral compression. The author has found that a Minerva orthosis provides ventral cranial base stability and enables symptomatic relief by preventing further skeletal deformity. Until the fundamental molecular anomalies can be addressed, the author feels that all intervention in the primary or acquired developmental form of basilar impression must be considered palliative. In contrast, acquired forms have a better prognosis because the underlying metabolic or biochemical abnormalities can be corrected.

27.7.6 Down Syndrome

Down syndrome is the most common chromosomal disorder, with an incidence of 1 in 700 live births. Atlantoaxial instability is the most prevalent craniocervical abnormality, present in up to 24% of patients, although it is symptomatic in fewer than 1% of affected individuals.² The early diagnosis and surgical treatment of craniocervical instability avert development of the severe neurologic deficits often triggered by minor trauma. Os odontoideum is a frequent finding in craniocervical junction instability associated with Down syndrome (► Fig. 27.4b).

It is now recognized that more than 50% of cases of craniocervical instability involve the occiput-atlas junction. Thus, atlantoaxial fixation without occipital incorporation can lead to neurologic disaster. The author mandates occipitocervical fixation in the presence of cranial settling, reducible basilar invagination, unstable os odontoideum, and anterior, posterior, or lateral cranial displacement of the spine.^{20,21,33,43,44} Atlantoaxial fusion is indicated if craniocervical instability is limited to the C1–C2 articulation. This author recommends atlantoaxial fusion if dynamic cervical radiographs indicate a predental space of more than 6 to 7 mm.⁴³ In older children (older than 10 years),

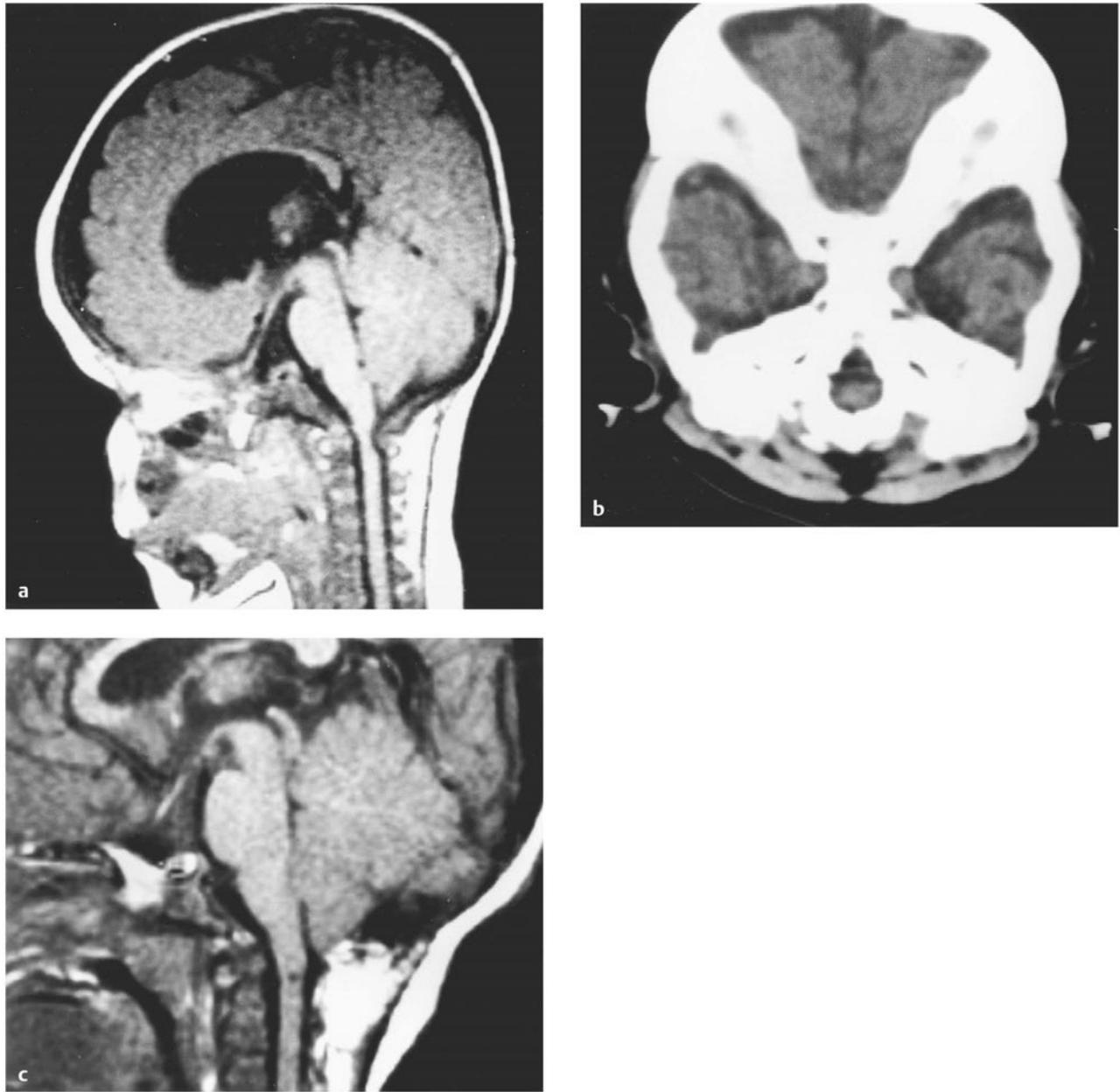


Fig. 27.10 (a) Lateral midsagittal T1-weighted magnetic resonance (MR) imaging of the brain and spinal cord in a 3-year-old child with achondroplasia. Repeated aspiration pneumonia and failure to thrive with weak arms brought her to neurosurgical attention. There is dorsal foramen magnum compression of the cervicomedullary junction. Note the hydrocephalus and the vertical orientation of the brainstem. (b) Axial computed tomographic scan through the plane of the foramen magnum visualizes the constriction in the sagittal as well as the coronal diameter. (c) Postoperative MR imaging in T1 mode following posterior fossa decompression and C1 laminectomy. A duraplasty was made. The decompression is satisfactory. Myelomalacia is seen at the C1 level.

transarticular screw fixation or atlas lateral mass screw–C2 pars screw with rod fixation can be performed safely.³⁴

27.7.7 Skeletal Dysplasias

These are divided into the following categories: (1) osteochondrodysplasia, (2) dysostosis, (3) chromosomal aberration, (4) idiopathic osteolysis, and (5) primary metabolic abnormal-

ities.^{5,24} These disorders include achondroplasia, spondyloepiphyseal dysplasia, multiple epiphyseal dysplasia, atrophic tonotropic dysplasia, Crouzon and Apert syndromes, neurofibromatosis, osteogenesis imperfecta, and a multicentric type such as the Hadju-Cheney form.^{19,24,40,41} In all, paramesial invagination (side to side) occurs together with a reduction in the sagittal diameter of the foramen magnum compounded by a dural shelf that forms through thickening and invagination

of the posterior dura into the cervicomedullary junction. This causes dorsal cervicomedullary compression in addition to the bony abnormality. Cervical stenosis may also be present in conditions such as achondroplasia and Morquio syndrome. Atlantoaxial instability occurs frequently in skeletal dysplasias. This is most common in children younger than 3 years of age and leads to cervicomedullary compromise, which typically manifests as sleep apnea and progressive spastic quadriparesis.²⁴ Definitive surgical treatment entails dorsal craniocervical decompression with duraplasty to address the cervicomedullary compression (► Fig. 27.10a-c). CSF shunting is required for hydrocephalus, which results from jugular bulb compression. The management of spondy-

loepiphyseal dysplasia is further complicated by a presentation in early infancy with associated atlantoaxial instability. Our approach has been to use a custom-built orthosis for external bracing until definitive surgical treatment can be performed by 3 to 4 years.

27.7.8 Segmentation Failures, Fusions, and Remnants at the Foramen Magnum and Atlas

In these developmental anomalies, bony projections from the clivus or lateral aspect of the foramen magnum cause central or

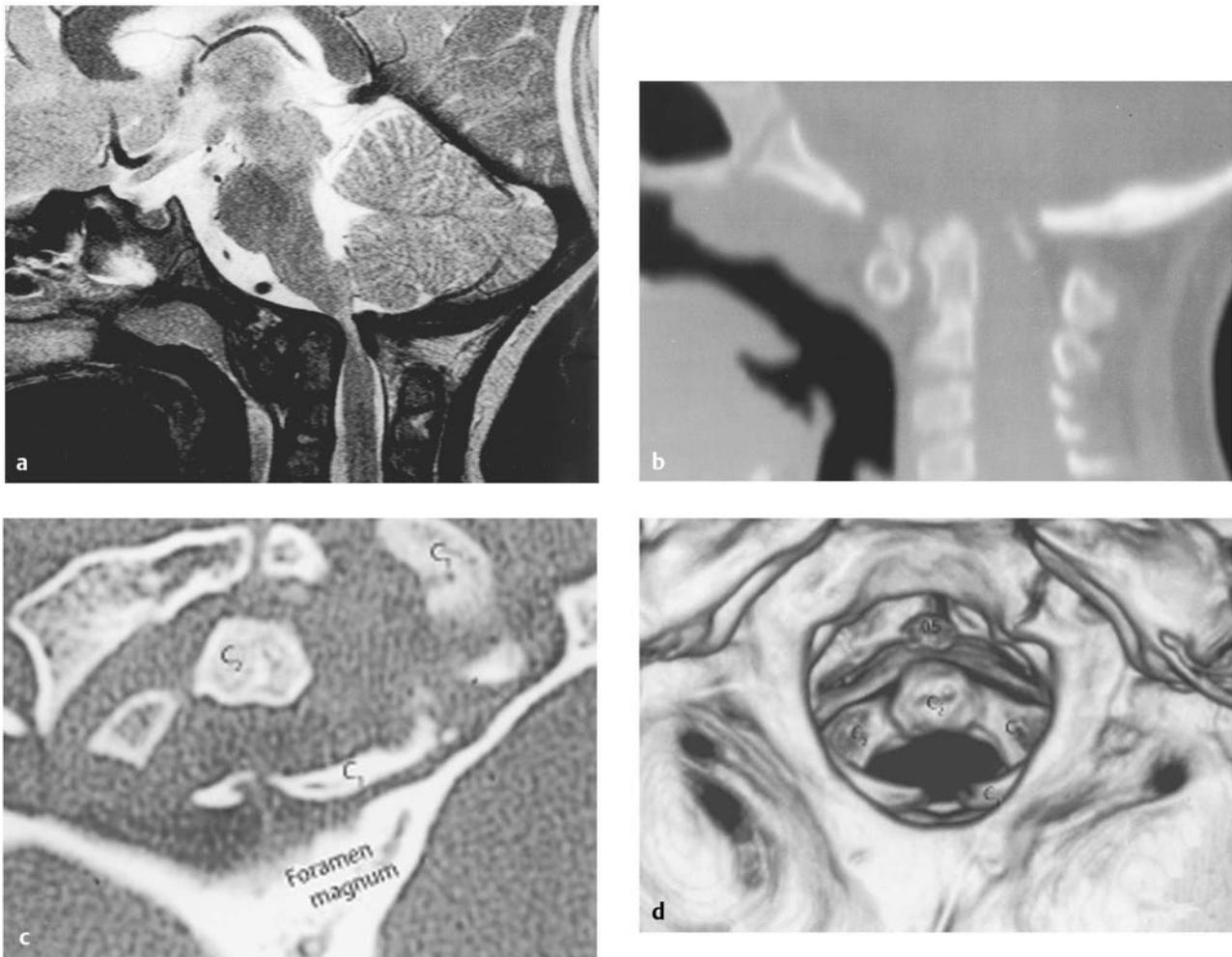


Fig. 27.11 (a) Midsagittal T2-weighted magnetic resonance imaging of the craniocervical junction. An hourglass constriction of the cervicomedullary junction is evident. The ventral component is the dorsal aspect of the axis body, and the dorsal component of the compression is the posterior arch of the atlas. A dystopic os odontoideum is evident. This patient presented with quadriparesis and lower brainstem dysfunction. (b) Midsagittal computed tomographic (CT) two-dimensional reconstruction of the craniocervical region. A dystopic os odontoideum resides above the anterior arch of the atlas between the inferior clivus and the ascended axis body. The posterior arch of the atlas has assumed a location just anterior to the posterior rim of the foramen magnum, causing severe compression of the cervicomedullary junction. (c) Axial CT through the plane of the foramen magnum. The anterior arch of the atlas is bifid, as is the posterior arch. The axis body is seen within the center of the spinal canal. (d) Three-dimensional CT scan of the craniocervical region viewed from within the foramen magnum. Note the bifid posterior arch of C1. Note also the separate os odontoideum and the C2 axis body in the center of the spinal canal.

paramesial invagination, respectively. High-resolution CT with three-dimensional reconstruction has facilitated greater recognition of the anomalies, which are most frequently seen in children between the ages of 2 and 16 years.⁴⁵

Atlas segmentation failures result in abnormal articulation between the clivus, atlas, and odontoid process. Other variations consist of unilateral or bilateral absence of the posterior arch of the atlas. An isolated bifid posterior arch of the atlas is commonly encountered and is not clinically significant. When it is associated with a bifid or bipartite anterior arch of the atlas, the two halves of the atlas vertebra act as a complex “Jefferson fracture.” The resultant lateral displacement leads to basilar invagination and caudal migration of the occipital condyles onto C2, causing neurovascular injury. Hence, bifid anterior and posterior arch of the atlas mandates surgical fixation beyond the age of 4 years. In the author’s experience, customized orthoses were used until the age of 3 to 4 years, after which occipitocervical fixation was undertaken if the pathologic anatomy persisted.

27.7.9 Odontoid Abnormalities

The most common odontoid abnormality is an os odontoideum. This term refers to an independent bone that is usually located in the position of the normal odontoid tip near the basiocciput and the area of foramen magnum, where it may ultimately fuse with the clivus. It is not an isolated dens but exists apart from a hypoplastic dens. Radiographically, an os odontoideum has smooth cortical borders and is separated by a variable gap from a small odontoid process. There is associated incompetence of the cruciate ligament and subsequent atlantoaxial instability (► Fig. 27.11a–d)

Os odontoideum is more common in association with ligamentous laxity and collagen disorders, as in Down syndrome and Morquio syndrome.^{15,46} Os terminale, on the other hand, represents failure of the secondary ossification center of the dens to fuse with the odontoid. It is not associated with mechanical instability because it lies above the transverse ligament. Os terminale is therefore not clinically significant.

There is now increasing evidence that os odontoideum is frequently associated with trauma at an early age.^{46–48} This may result in either an odontoid fracture or a stress injury at the neck of the odontoid process, leading to subsequent separation of the bone and the formation of a sequestrum. In the author’s series, a fully developed odontoid process was seen in a significant number of children before an injury that occurred between the ages of 1 and 4 years. An os odontoideum subsequently developed in these same children.²

The movement of an os odontoideum is individual in each child and hence must be carefully studied before treatment is undertaken. It is not uncommon for an os odontoideum to be recognized in a child following minor trauma when lateral cervical spine radiographs are taken. If there are abnormal excursions of the craniocervical junction, ligamentous laxity has already taken place, and this author mandates that surgical fixation should be undertaken.

Pearls

In this authors’ experience:

- It is not uncommon for children with craniocervical abnormalities to present with basilar migraine, dysphagia, sleep apnea, the syndrome akin to central cervical spinal cord dysfunction, and scoliosis.
- Torticollis in children may represent craniocervical abnormalities. Three-dimensional CT is required.
- When unexplained neurologic symptoms and signs are associated with craniocervical abnormalities, vertebral angiography should be performed with dynamic motion studies.
- Crown halo application in children requires the placement of six to eight pins beneath the cranial equator. Finger tightening of the pins is used before 2 years of age. At 5 years of age, 4 lb of torque pin pressure is used. The “adult” 8-lb torque is applied in children past 12 years of age.

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28 Congenital Intraspinal Cysts

Andrew B. Foy and Bruce A. Kaufman

Congenital cystic lesions of the spine are rare entities in children. These developmental lesions are often slow-growing and can present in childhood or early adulthood with a range of symptoms related to nerve root or spinal cord compression. The lesions are readily identified on magnetic resonance (MR) imaging. Although they are often identified as isolated lesions, many congenital cysts are associated with various forms of spinal dysraphism and vertebral column abnormalities.

Arachnoid cysts are benign arachnoid diverticula filled with spinal fluid that can occur along the entire neuraxis. Spinal arachnoid cysts occur less frequently than intracranial arachnoid cysts. Little has been reported on the incidence of spinal arachnoid cysts in the general population. A review of children undergoing routine MR imaging of the brain found that intracranial arachnoid cysts were present in 2.6% of the children, but it is presumed that spinal arachnoid cysts occur much less frequently.¹ In a retrospective review, 25% of arachnoid cysts that required surgical intervention were intraspinal.²

Neurenteric cysts are endodermal inclusion cysts of the spinal canal. Numerous names have been given to this entity in the literature, and all of them describe cystic structures of endodermal origin. Frequently used names in the literature include *neurenteric cyst*, *archenteric cyst*, *intestionoma*, *enterogenous cyst*, *dorsal enteric fistula*, and *neurenteric canal remnant*.³ For the purposes of this chapter, the term *neurenteric cyst* will be used.

Spinal dermoid and epidermoid cysts are congenital tumors thought to arise from abnormal rests of ectodermal cells. These lesions can occur in the intraspinal or intracranial space. In a large series published by Lunardi et al, spinal dermoid and epidermoid tumors represented 2.2% of all surgically resected primary spinal tumors.⁴ The lesions commonly present in early childhood and account for 17% of all primary spinal tumors diagnosed within the first year of life.⁴ Dermoid tumors are more common in the spine, whereas epidermoid tumors are more commonly cranial in location.

28.1 Arachnoid Cysts

Although intracranial arachnoid cysts are more prevalent in males, a similar distribution has not been found for spinal arachnoid cysts. Spinal arachnoid cysts have on rare occasion been found to be familial.⁵⁻⁷ These lesions have also been reported to be associated with genetic conditions, including hereditary distichiasis, neurocutaneous melanosis,⁸ and Noonan syndrome.⁹ Spinal arachnoid cysts are also prevalent in patients with spinal dysraphism, most frequently presenting in those with open neural tube defects or split-cord malformations.¹⁰

Arachnoid cysts have been reported in the extradural and intradural space. Rare cases of intramedullary arachnoid cysts have also been reported.^{11,12} The majority of these cysts are solitary and located within the thoracic spine, although cases of multiple spinal arachnoid cysts have been reported.¹³ Arachnoid cysts, unlike neurenteric cysts, are more likely to be located dorsal to the spinal cord.

The mechanism that leads to the development of a spinal arachnoid cyst is not entirely known. There are likely multiple causes for these lesions. Intradural arachnoid cysts have been postulated to arise from congenital diverticula of the arachnoid. Extradural arachnoid cysts are thought to arise from the herniation of arachnoid through a weakness in the spinal dura.¹⁴ Perret et al suggested that spinal arachnoid cysts are derived from an expansion of the septum posticum, an arachnoid partition dividing the posterior spinal subarachnoid space.¹⁵ This theory is supported by the frequent reports of congenital intradural and extradural arachnoid cysts found dorsal to the spinal cord.

Some spinal arachnoid cysts likely arise secondary to inflammation, trauma, or subarachnoid scarring.¹⁶⁻¹⁸ Spinal arachnoid cysts in children with myelomeningocele have been postulated to result from extensive subarachnoid scarring and alterations in the flow of spinal fluid, and they may be acquired lesions.¹⁰

A number of theories have been proposed to account for the growth and progression of spinal arachnoid cysts. The most common theory states that a ball valve mechanism exists between the cyst and subarachnoid space, allowing the one-way flow of spinal fluid into the arachnoid cyst.^{19,20} Other investigators have postulated that an osmotic gradient exists between the cyst and extracystic space, or that there is fluid hypersecretion by the cells lining the cyst wall.²¹

The symptoms related to spinal arachnoid cysts can be nonspecific and subtle. Symptoms are usually the result of compression on the spinal cord or spinal nerve roots. About 50% of children with arachnoid cysts present with pain.^{22,23} Children often report back pain or radicular arm, thoracic, or leg pain. Other common symptoms include motor weakness, gait instability, sensory disturbances, and urinary incontinence or retention. Symptoms are often aggravated by upright positioning, coughing, and straining as fluid is forced into the arachnoid cyst or intraspinal pressures fluctuate. Children may also present with unexplained scoliosis or kyphosis.²⁴ Physical examination often reveals evidence of a myelopathy or radiculopathy, depending on the location and level of the lesion. Children may also have point tenderness of the midline spine or palpable evidence of scoliosis.

Plain radiographs of the spine may be entirely normal or show subtle evidence of an arachnoid cyst. The presence of kyphoscoliosis may be apparent on radiographs. There may be nonspecific findings of an underlying mass, including scalloping of the vertebral body, thinning of the pedicles, and widening of the interpedicular distance. Computed tomography (CT) after myelography can show evidence of cord compression and the flow of contrast around or into an arachnoid cyst, but this study has largely been supplanted by MR imaging as the diagnostic test of choice.²⁵

MR imaging reveals a cystic structure with fluid that is isointense to spinal fluid on T1- and T2-weighted images^{25,26} (► Fig. 28.1). Occasionally, increased protein in the cyst will cause a T1-weighted signal slightly higher than that of (► Fig. 28.1c). MR imaging has the ability to identify both the lesion and the degree of spinal cord and nerve root compression. The cyst wall usually is smooth and shows no evidence of

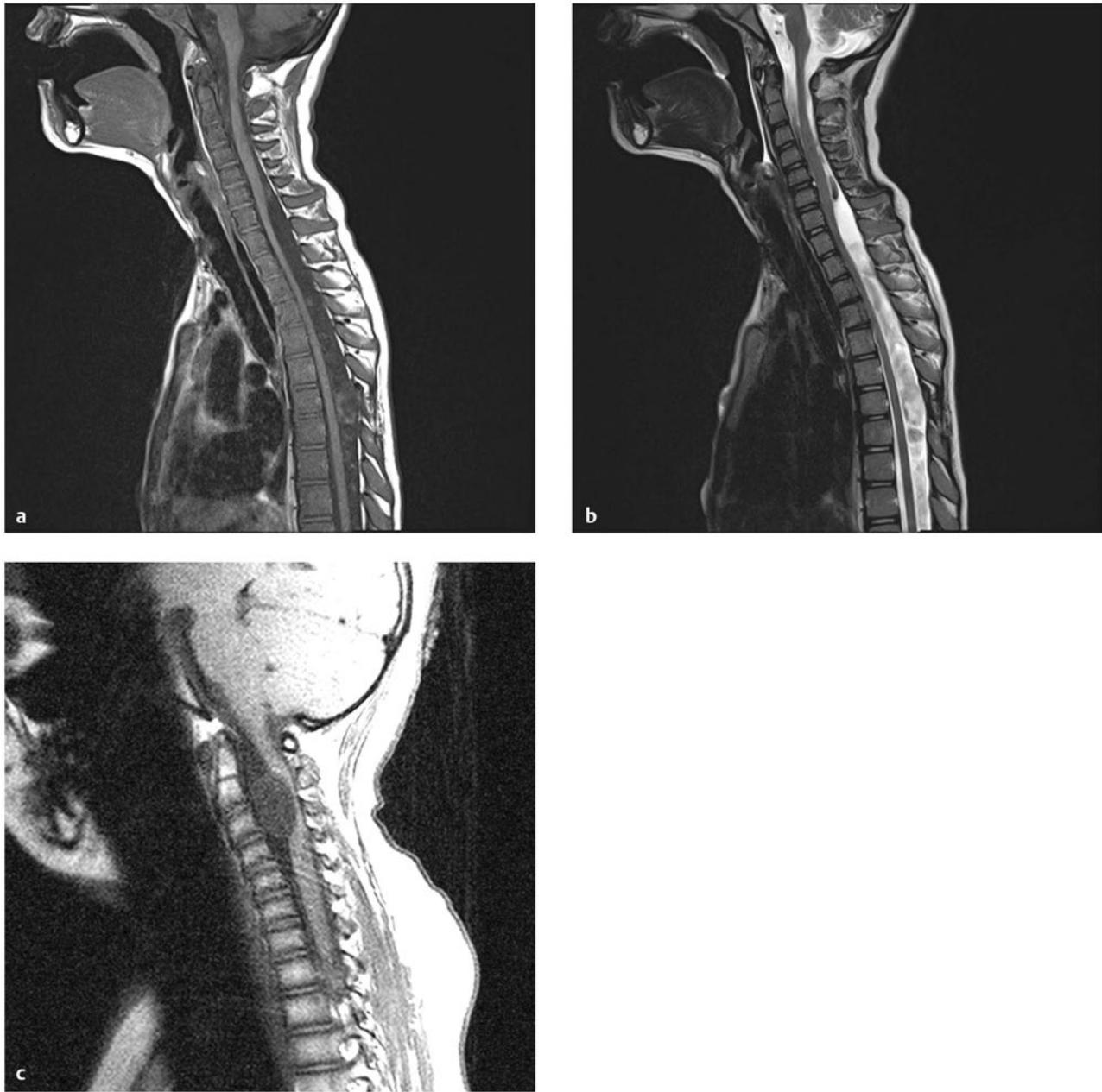


Fig. 28.1 Arachnoid cyst. (a) Arachnoid cysts are typically located dorsal to the cord, like this cervicothoracic lesion, with the cyst fluid slightly hypointense to cerebrospinal fluid (CSF) on T1-weighted sequences. Mild cord compression is seen. (b) On the T2-weighted sequence, the cyst fluid is hyperintense to CSF, and flow voids can be seen above and below the cyst, helping to define its extent. (c) The surgically proven arachnoid cyst shown is unusual in its location, anterior to the cord, and in its signal characteristics, which are slightly hyperintense to those of CSF. The flow void artifact (bottom of cyst) helps to define the lower cyst margin.

abnormal contrast enhancement. More recently, cine MR imaging has been used to show abnormal spinal fluid flow at the cyst wall boundary and dynamic cord compression.²⁷

Pathologically, these lesions are composed of a collagenous membrane lined by a flattened meningotheial cell layer. Focal areas of meningotheial cells may be present. Immunohistochemical labeling studies are often unremarkable.²⁸

The treatment of arachnoid cysts can range from simple observation to surgical fenestration or resection, although surgical

fenestration or excision of these lesions has been the treatment of choice for many years. Observation may be chosen for those cysts that are discovered incidentally in children without symptoms referable to the cyst.

When surgical treatment is chosen, a posterior approach is usually preferred because the majority of these cysts are dorsal to the spinal cord. Laminoplasty is often performed rather than laminectomy in an attempt to reduce the incidence of postoperative spinal deformity.²⁹ Intraoperative neurophysiologic

monitoring, including somatosensory evoked potentials and motor evoked potentials to monitor the function of the spinal cord during cyst excision, can also be employed.

For extradural arachnoid cysts, the cyst wall should be present immediately after the laminotomy has been performed. The cyst wall is dissected free of the surrounding tissues, and in most instances a small rent will be visualized along the dorsal surface of the dura. The cyst wall is completely resected, and the dura is closed with sutures. Intradural exploration can be performed if there is concern for intradural extension of the cyst. Rare instances of extradural arachnoid cysts without a clear intradural connection have been reported.³⁰

For intradural arachnoid cysts, the dura is opened and tacked back to expose the cyst. The cyst is carefully removed from the dural surface, spinal cord, and nerve roots under magnified vision (i.e., an operating microscope). When the cyst wall is densely adherent to the spinal cord or nerve roots, those parts of the wall are left behind. For ventral cysts, wide fenestration of the cyst into the subarachnoid space is often performed because it is difficult to access the entire cyst without putting significant traction on the spinal cord.³¹

Cyst-to-subarachnoid space shunting or cyst-to-pleura shunting is a viable surgical alternative.¹⁰ More recently, investigators have utilized intrathecal endoscopy to minimize the incision and bone removal; however, the utility of this approach is unclear.^{32,33} Percutaneous image-guided aspiration of spinal arachnoid cysts has been reported.^{34,35}

Outcomes of surgical treatment are good. Bond et al recently reported that 87% of patients had symptomatic improvement after surgical fenestration or resection of a spinal arachnoid cyst.¹¹ The recurrence rate of arachnoid cysts treated with excision or wide fenestration is low.^{11,31} Although short- and intermediate-term results have been good, some studies have suggested late worsening following the treatment of spinal arachnoid cysts.³⁶

28.2 Neurenteric Cysts

Neurenteric cysts are distinctly uncommon, accounting for roughly 1% of spinal neoplasms.^{37,38} Older retrospective studies have shown a slight male predominance.^{38,39} However, more recent studies have shown widely varying distributions.^{37,40–42} Patients can present with symptoms at any time during childhood or early adulthood.

The majority of spinal neurenteric cysts are located in the intradural extramedullary space ventral to the cervical or thoracic spinal cord. This is likely due to their origin from the foregut. Fewer than 5% of reported cases are wholly or partially intramedullary.⁴³ A distinct minority of these lesions have been identified in the lumbar region.⁴⁴

Although neurenteric cysts can occur in isolation, it is not uncommon for them to occur with other congenital spinal abnormalities. Neurenteric cysts have been found in association with various vertebral column anomalies, including partial sacral agenesis, block vertebrae, hemivertebrae, Klippel-Feil anomaly, and butterfly vertebrae.^{37,40,45} In addition, syringomyelia, split-cord malformations, spinal cord lipomas, and dermal sinus tracts have been found in association with neurenteric cysts.^{37,45,46} Although they are generally benign

in nature, dissemination and malignant transformation of these lesions have been reported.^{47,48}

The embryologic origin and pathogenesis of spinal neurenteric cysts are not entirely clear. Incomplete separation of the foregut from the notochord during early embryonic development seems to be an integral component in the development of a neurenteric cyst. During the third week of embryonic development, the mesoderm along the midline of the embryo coalesces to form the notochord. Also during the third week, intercalation of the notochord into the endoderm occurs briefly, and a primitive neurenteric canal forms connecting the endoderm and ectoderm through the notochord.⁴⁹ Neurenteric cysts likely are derived from abnormalities occurring during this early developmental period. Macdonald et al reviewed four theories of neurenteric cyst pathogenesis.⁴⁹ These theories include splitting of the notochord with an aberrant persistent connection between endoderm and ectoderm, incomplete or abnormal ex-calcation of the notochord, ectopic spinal rests of endoderm, and persistence of the primitive neurenteric canal.

A range of symptoms have been associated with spinal neurenteric cysts. Many present with the same constellation of symptoms seen in children with arachnoid cysts, including back pain, radicular pain, paresthesias, weakness, gait changes, and changes in bowel or bladder function. These symptoms generally result from compression on the neural and vertebral elements. Uncommon presentations of neurenteric cysts include unexplained fever,⁴⁰ cyst rupture with resultant chemical meningitis and arachnoiditis,⁵⁰ recurrent bacterial meningitis,⁵¹ and intracystic hemorrhage.⁵²

Plain radiographic images are of limited utility in the diagnosis of a neurenteric cyst. However, these studies can be useful in documenting the range of vertebral anomalies that are commonly found in conjunction with these lesions. Holmes et al noted that 77% of children with neurenteric cysts had abnormal plain radiographs.³⁹

MR imaging is the diagnostic test of choice (► Fig. 28.2). The signal characteristics of the cyst fluid are variable and depend largely on the protein content of the cyst fluid.⁵³ In general, the cyst fluid is isointense to slightly hyperintense compared with spinal fluid on T1- and T2-weighted imaging sequences. The cyst itself is often thin-walled and shows no evidence of enhancement. The degree of nerve root and spinal cord compression can also be ascertained from MR imaging.

Grossly, these lesions may be thin-walled or thick-walled. The cyst fluid can vary from clear to quite turbid. Light microscopy shows evidence of an epithelial layer, with goblet cells, ciliated cells, and squamous cells lying on a basement membrane. Immunocytochemical studies show cytokeratin and epithelial membrane antigen positivity in the endothelial cells.⁴⁹ Although the epithelium is presumed to be of gastric origin, Morita et al, using electron microscopy, found that the features of the epithelium of the wall of a recurrent neurenteric cyst were more consistent with a respiratory origin.⁵⁴

As for arachnoid cysts, surgical resection is the primary treatment modality for symptomatic neurenteric cysts. However, these lesions are often ventral in location, making surgical access difficult. Total excision of the cyst with decompression of the spinal cord and nerve roots is the goal of surgery. Subtotal resection is often necessary to avoid damage to the spinal cord and nerve roots when the cyst is highly adherent to these

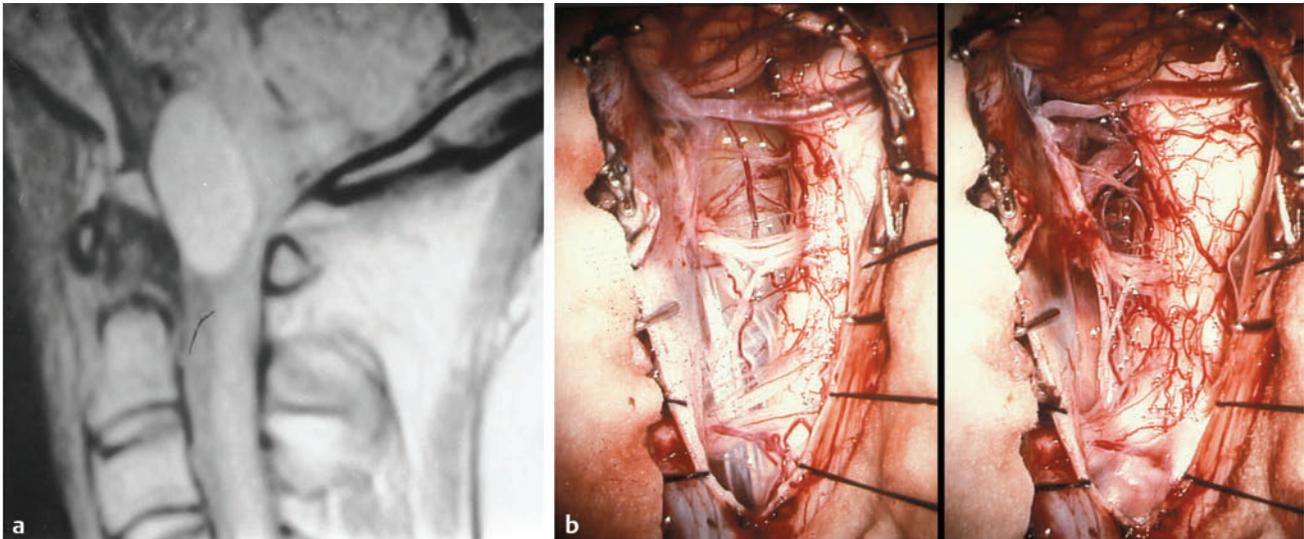


Fig. 28.2 Neurenteric cyst. (a) The neurenteric cyst in this sagittal T1-weighted magnetic resonance image is typical in location (anterior to the cord) and signal characteristics (slightly hyperintense). (b) Intraoperative view of the anteriorly placed, well-defined neurenteric cyst, surrounded by the vessels and nerves of the upper cervical spine, before and after complete resection. (From Menezes AH. Tumors of the craniovertebral junction. In: Winn HR, ed. Youmans Neurological Surgery. 6th ed. Philadelphia, PA: W. B. Saunders; 2011:3114–3130.)

structures or when significant manipulation on the cord would be required to fully access an anterior lesion.

Both posterior and anterior approaches to these lesions have been reported. The posterior approach avoids the extensive bone work and fusion that may be required for anterior approaches, but ventrally located cysts are difficult to access or completely resect from a posterior approach. When ventrally located cysts are approached from a posterior laminoplasty, care must be taken to avoid undue traction on the spinal cord and nerve roots.^{37,40} The dentate ligaments can be sectioned to allow improved access to the ventral cord. Anterior approaches are technically more challenging, require more bone removal, and are likely to destabilize the spine, necessitating a fusion procedure. However, anterior approaches to ventrally located cysts offer more direct visualization and usually allow greater resection of the cyst wall.^{50,55,56}

Outcomes after the surgical resection of neurenteric cysts have been generally good. The majority of patients clinically improve following surgical intervention.^{37,40} More difficult to assess are the long-term outcomes and incidence of cyst recurrence. Recurrence of neurenteric cysts, especially incompletely resected lesions, has been reported. Chavda et al reported a 37% long-term recurrence rate in eight patients over a 30-year period.⁵⁷ The lesions were slow to regrow, with recurrences noted 4 to 14 years after the initial surgery. Other authors have found recurrence to be relatively uncommon.^{39,58}

28.3 Dermoid and Epidermoid Cysts

Dermoid and epidermoid tumors of the spine are found most commonly in the lumbar region and are usually intradural and extramedullary. In a series of 62 tumors in the region of the

conus medullaris and cauda equina, dermoid and epidermoid tumors represented nearly one-third of the total.⁵⁹ There are conflicting reports in the literature with regard to the male and female distribution of these lesions; however, the most recent series has shown equivalent rates among males and females.⁶⁰

Classically, spinal dermoid and epidermoid cysts have been thought to arise from an abnormal inclusion of ectodermal cell rests during closure of the neural tube between the third and the fifth week of gestation. Although there is little scientific evidence, some believe that the timing of the abnormal implantation of ectodermal cells determines whether a dermoid or an epidermoid tumor develops. The implantation of less differentiated ectodermal cells early in fetal life leads to the development of dermoid tumors, whereas the later implantation of ectodermal cells leads to more differentiated epidermoid tumors.^{60,61}

These spinal lesions can be iatrogenic. There is good evidence that the introduction of cutaneous cells during procedures such as lumbar puncture can lead to the development of dermoid tumors.⁶² The delayed development of dermoid tumors has also been reported in children with myelomeningocele.^{63,64} Although the dermoid tumors may be due to the inclusion of dermal elements during closure of a myelomeningocele, ventral dermoid tumors remote from the site of myelomeningocele closure in these children are likely the result of congenital rests of ectoderm cells.

Inclusion cysts of the spine are most commonly located in the lumbar region and are generally dorsal intradural and extramedullary lesions. Partially intramedullary or completely intramedullary dermoid tumors have been reported.^{60,65,66} Many congenital spinal and vertebral anomalies have been reported in association with spinal dermoids and epidermoids. Myelomeningocele, split-cord malformation, syringomyelia, and vertebral column fusion anomalies have been reported with

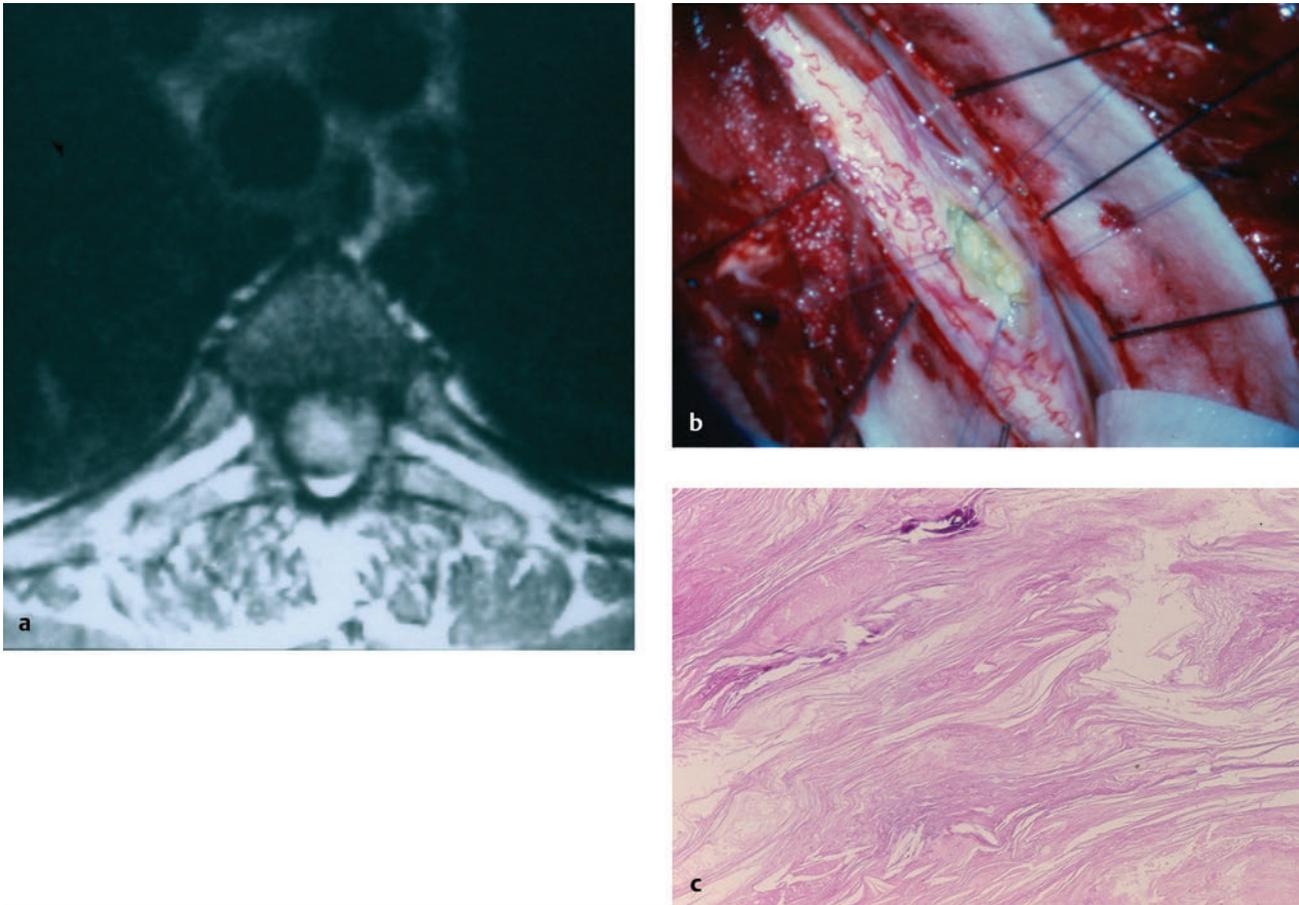


Fig. 28.3 Epidermoid cyst. (a) This epidermoid cyst is hyperintense on axial T2-weighted imaging. (b) Intraoperatively, the lesion was found to be intramedullary, located along the posterior-lateral aspect of the spinal cord (pia retracted with Prolene suture). (c) The membrane showed typical stratified, keratinized squamous epithelium.

intraspinal inclusion tumors. Dermal sinus tracts are particularly common in children with spinal dermoids.^{60,67}

Children harboring intraspinal dermoid or epidermoid tumors can have a range of symptoms. Many children present with symptoms that mimic the typical manifestations of spinal arachnoid or neurenteric cysts, including back and radicular pain, weakness, sensory disturbance, and bladder dysfunction. Scoliosis and kyphosis can occur in these patients. In patients with an associated dermal sinus tract, the presenting symptoms may be a consequence of local infection of the dermal sinus, frank meningitis, or spinal empyema.⁶⁸

Although a detailed neurologic examination is warranted to look for evidence of a myelopathy or radiculopathy, examination of the back is also important. Common cutaneous findings on examination of the spine include dimples above the gluteal cleft, dermal sinus tracts, hairy patches, and hemangiomas.

As for other types of spinal cysts, MR imaging is the test of choice for delineating these lesions. Epidermoid tumors tend to have signal characteristics similar to those of spinal fluid, with T1-weighted hypointensity and T2-weighted hyperintensity (► Fig. 28.3). Conversely, dermoid tumors often are hyperintense on T1-weighted images and have low signal intensity on

T2-weighted images. However, it should be noted that the imaging of dermoid and epidermoid tumors is highly variable.^{69,70} Diffusion-weighted imaging sequences have shown some early success in distinguishing dermoid and epidermoid cysts from other spinal lesions. Diffusion-weighted imaging sequences often show restricted diffusion in dermoid and epidermoid tumors, whereas arachnoid cysts have no such diffusion restriction.⁷¹

On gross examination, dermoid and epidermoid tumors are whitish yellow in appearance. The tumor capsule is filled with a soft white tissue composed of keratinized debris. Dermoids also have evidence of adnexal structures, including hair and hair follicles, and occasionally have calcium deposits. Epidermoid cysts on microscopic examination are composed of a layer of stratified squamous epithelium (► Fig. 28.3c). Dermoid cysts have a similar stratified squamous epithelium with interspersed sebaceous glands and hair follicles.

Surgery is the primary means of treating symptomatic spinal dermoid and epidermoid tumors. As the majority of these lesions are dorsal to the spinal cord and cauda equina, a posterior approach is usually indicated (► Fig. 28.3b). The goal of surgery is complete removal of the cyst and decompression of the spinal cord and nerve roots. The epithelial lining of these lesions is

often highly adherent to the spinal cord and nerve roots. Care must be taken to achieve as complete a resection as possible without damaging the neural tissues. Most case series have reported only a 40 to 50% rate of visual gross total resection at the time of surgery.^{4,72}

Surgical resection is often successful in stabilizing or improving preoperative symptoms. In recent series, 80 to 90% of patients stabilized or improving following surgical intervention.^{60, 72} Aseptic or cholesterol meningitis is a frequent postoperative complication. Some authors have advocated multiple lumbar punctures to treat postoperative aseptic meningitis.⁴ Long-term tumor control is good even when an incomplete resection is achieved. These lesions are slow-growing, and frequently, recurrence is seen many years after the initial resection.^{4,60,72}

Pearls

- Congenital intraspinal cysts are rare lesions that often present with subtle symptoms, including unexplained back or extremity pain.
- MR imaging is the diagnostic test of choice for detecting congenital intraspinal cysts.
- Complete resection of the cyst is frequently the treatment of choice, although complete resection may not be safe if there is significant adherence of the cyst to the surrounding neural structures.
- Cyst recurrence is fairly uncommon, but close observation is warranted following surgical treatment for any congenital intraspinal cyst.

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29 Congenital Vertebral Anomalies

Douglas Brockmeyer

Congenital vertebral anomalies are relatively common disorders, ranging from simple, asymptomatic “block” vertebrae to complex combinations of anomalies involving multiple vertebral levels. They can occur anywhere from the craniovertebral junction to the coccyx. This chapter covers congenital vertebral anomalies from the cervical spine to the sacrum. Congenital vertebral anomalies may be associated with other birth defects, and awareness of these associations is important. To manage patients with congenital vertebral anomalies effectively, a firm grasp of the relevant embryology, classification, natural history, clinical evaluation, and treatment principles is essential.

29.1 Historical Background

Although spinal deformities have been recognized in the medical literature for centuries, it was not until the early part of the 20th century that the first vertebral anomaly syndromes were characterized. In 1912, Klippel and Feil reported a patient with the triad of low posterior hairline, short neck, and reduction in cervical spine motion, thus providing the first description of the syndrome that now bears their names.¹ A little over a decade later, Foix and Hillemand provided a classification scheme for caudal agenesis based on the extent of sacral and coccygeal involvement.² Significant advancements in the description and understanding of vertebral anomalies occurred with the development of spinal radiographs in the middle of the century, and extensive effort over the past 20 years by many authors, notably Winter et al,^{3,4} McMaster and Ohtsuka,⁵ and Pang et al.^{6–9} has provided tremendous insight into the pathogenesis, treatment, and prognosis of these disorders.

29.2 Embryogenesis

The sequential stages of the development of the spine have been extensively discussed in prior texts⁷ and will be only briefly reviewed here. The first six embryonic weeks set the stage for early vertebral development in a process known as primary neurulation. In that period, also known as the mesenchymal stage, the notochord develops in the first few embryonic weeks from cells within the Hensen node.¹⁰ Somitic mesodermal cells migrate from a position just caudal to the Hensen node and ultimately lie just lateral to the midline notochord. These cells coalesce into paired somites in a rostral to caudal direction, all under the influence of the notochord, the neural tube, homeobox genes, and cell adhesion proteins.^{11–13} The somites ultimately divide into sclerotomes and dermomyotomes, with each of the bilaterally paired sclerotomes giving rise to a single vertebral body and single set of posterior elements during a migrational phase in the fourth and fifth embryonic weeks.^{12–14}

Although this process of primary neurulation accounts for the formation of the vertebral column and spinal cord down to the lumbosacral junction, most sacral and coccygeal vertebrae develop from the caudal eminence in a poorly understood process called secondary neurulation.¹⁰ The caudal eminence is a

mass of undifferentiated cells at the caudal end of the primary neural tube.⁶ Secondary neurulation begins at approximately the fourth embryonic week and is responsible for the formation of the spinal cord, nerve roots, and vertebral column of the sacral and coccygeal areas.^{15,16} New insights into the complex manifestations of secondary neurulation are provided by Pang et al.^{8,9}

During the sixth embryonic week, the chondrification stage begins with the formation of three paired chondrification centers within a vertebra. One set of chondrification centers develops anteriorly to form the vertebral body, and two sets develop posteriorly to form the posterior elements. This process develops in a cranial and caudal direction from the cervicothoracic junction and is responsible for rapid vertebral column growth.¹⁷ It culminates at approximately the ninth embryonic week. Ossification of the cartilaginous elements begins shortly thereafter and ultimately ends somewhere between the 14th and 18th years of life.^{18,19} The intervertebral disk develops from tissue derived from perinotochordal mesenchymal cells and begins its formation in the chondrification stage.¹²

29.3 Epidemiology

Accurate statistics regarding congenital vertebral anomalies are difficult to come by because many patients are asymptomatic and the anomalies remain undiscovered. Incidence rates are also difficult to gather because many cases are discovered incidentally and never evaluated further. Furthermore, estimates are difficult to obtain in young children because of radiographic variations. At an early age, vertebrae have partially ossified centra and arches that may be confused with congenital vertebral anomalies.^{18,20}

An estimated 5% of fetuses have vertebral anomalies.²¹ About 3% of the normal population have one or two more than the usual 7 cervical, 12 thoracic, 5 lumbar, and 5 sacral vertebrae; approximately 2% of the population have one less.¹⁸ About 7 in 1,000 individuals in the general population have a congenital union of two or more cervical vertebrae.^{22,23} The incidence of caudal agenesis in Sweden was reported as 1 in 7,500 births, a number similar in magnitude to the 1 in 4,000 incidence found in Chicago.²⁴ The incidence of scoliosis of more than 10 degrees was reported as a little over 1% for students in Beijing,²⁵ but a slightly higher figure of 2 to 3% has been cited for idiopathic scoliosis in skeletally immature children in the United States.²⁶

29.4 Etiology

Congenital vertebral anomalies commonly result from abnormal development during the first trimester of pregnancy.²⁷ The nature and timing of the insult to the embryonic vertebral column determine the type of congenital abnormality that is produced. Hemivertebrae and hypoplastic vertebrae arise during the mesenchymal stage, with a disruption of the primary chondrification centers and a pairing defect of the responsible sclerotomes, respectively.¹⁷ Some authors have proposed that

vertebral body hypoplasia and aplasia, both common causes of kyphotic abnormalities, arise during the chondrification stage, possibly as a consequence of absent centrum vascularization.^{17, 19,28} Environmental factors, including infections such as tuberculosis, can also result in hypoplastic vertebrae and congenital scoliosis.²⁷

The etiology of osseous malformations in the cervical spine is probably multifactorial.²⁹ Autosomal-dominant inheritance of cervical ribs has been reported,³⁰ and the congenital cervical fusions occurring with abnormalities such as the Apert and Crouzon syndromes are probably based on autosomal-recessive and autosomal-dominant inheritance patterns, respectively.³¹ Genetic inheritance does not account for many of these lesions, however, and there is some evidence to suggest that congenital vertebral anomalies result from vascular occlusions during development.

Some authors have suggested a subclavian artery supply disruption sequence to explain the pathogenesis of Klippel-Feil and other vertebral anomalies.^{29,32} They hypothesize that cervical fusions result from the disruption of intersegmental vessels arising from the vertebral arteries at the time of resegmentation of the sclerotomes. Specific refinements of this hypothesis have been forwarded by Tredwell et al,³³ who reported that the fetal alcohol syndrome variant of the Klippel-Feil anomaly is always associated with a single level of congenital fusion. In contrast, other cases of Klippel-Feil have only a 20% rate of single-level fusion. They relate this finding to a specific teratogenic insult occurring between the 24th and 28th days of embryonic life.³³

Vascular occlusion may be only one of several causes of congenital vertebral anomalies. Chandraraj³⁴ described anatomical specimens in which failure of development of the zygapophysial joint appeared to cause vertebral body fusions, or block vertebrae. He suggested that in some cases, the condition was probably linked to a defect of an inductor substance (e.g., the neuraxis) that influences normal morphogenesis of the vertebral arch in the embryonic period.

The etiology of more complex vertebral anomalies, such as congenital vertebral dislocation, segmental spinal dysgenesis, and medial spinal aplasia, is currently poorly understood.^{3,16,35, 36} Dias and colleagues³⁵ have proposed that congenital vertebral dislocation arises as a result of early embryonic buckling that affects all vertebral elements in a segmental fashion between the fourth and sixth embryonic weeks.

29.5 Classification

Congenital anomalies of the spine have previously been classified according to their anatomy, pathology, or embryology.^{20,37, 38} Because a comprehensive classification scheme encompassing all types of vertebral anomalies is not available, they have traditionally been divided into disorders of vertebral formation, vertebral segmentation, or a combination of both (see box “Classification of Congenital Vertebral Anomalies” (p.365)). Many of the underlying genetic and embryologic abnormalities are only beginning to be understood. Our understanding of many disorders, including congenital vertebral dislocation, segmental spinal dysgenesis, and medial spinal aplasia, is evolving.^{16,35,36,39} This chapter relies primarily on the traditional

classification scheme and discusses the findings of the more complex disorders in a separate section.

Classification of Congenital Vertebral Anomalies

- Disorders of formation
 - Wedge vertebrae
 - Hemivertebrae
 - Caudal agenesis
 - OEIS syndrome
 - VACTERL syndrome
- Disorders of segmentation
 - Block vertebrae
 - Segmental bars
- Combination disorders
- Special disorders
 - Congenital vertebral dislocation (deformation disorder)
 - Segmental spinal dysgenesis (probable disorder of formation)
 - Medial spinal aplasia (probable disorder of formation)

Abbreviations: OEIS, omphalocele, cloacal exstrophy, imperforate anus, and spinal deformities; VACTERL, vertebral anomalies, ano-rectal malformations, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies.

Disorders of vertebral formation are regarded as failures in development of any part of the vertebral column. They may be either complete or partial and may be unilateral or bilateral. Incomplete formation of a vertebral body results in a wedge vertebra, with one side hypoplastic and with an asymmetric appearance. If one pedicle and the adjacent vertebral body are absent, a hemivertebra results. A hemivertebra can be further classified depending on whether it is fused to one or both adjacent vertebrae. An *unsegmented hemivertebra* is fused to the adjacent vertebrae above and below, a *partially segmented hemivertebra* is fused to one vertebra above or below, and a *segmented hemivertebra* is separated by a disk space from each adjacent vertebra. In the sacrococcygeal area, a more complex example of these disorders is the caudal agenesis syndrome.

Disorders of vertebral segmentation give rise to failures of vertebral separation and different degrees of intersegmental fusion (► Fig. 29.1). These disorders include block vertebrae and unilateral unsegmented bars. Block vertebrae may be the best example of a segmentation failure resulting from the failure of a somite segment to separate into cephalic and caudal halves, creating one large block with no intervening disk. A similar defect occurring on one side of the developing spinal column results in the formation of a unilateral unsegmented bar. The term *unsegmented bar* describes a bony bar that fuses the disk space and facet joints of one or more adjacent vertebral levels. The fusion may exist in the anterior spinal column, posterior spinal column, or both and may exist alone or in combination with other disorders. Vertebral growth proceeds on the segmented side only, a condition that often leads to severe scoliosis. A segmentation failure across the anterior portion of adjacent segments with normal development of the posterior portion of the vertebra leads to progressive kyphosis. Lateral segmentation anomalies are presumed to begin in the membranous and cartilaginous phases of vertebral development.¹⁷ In contrast,

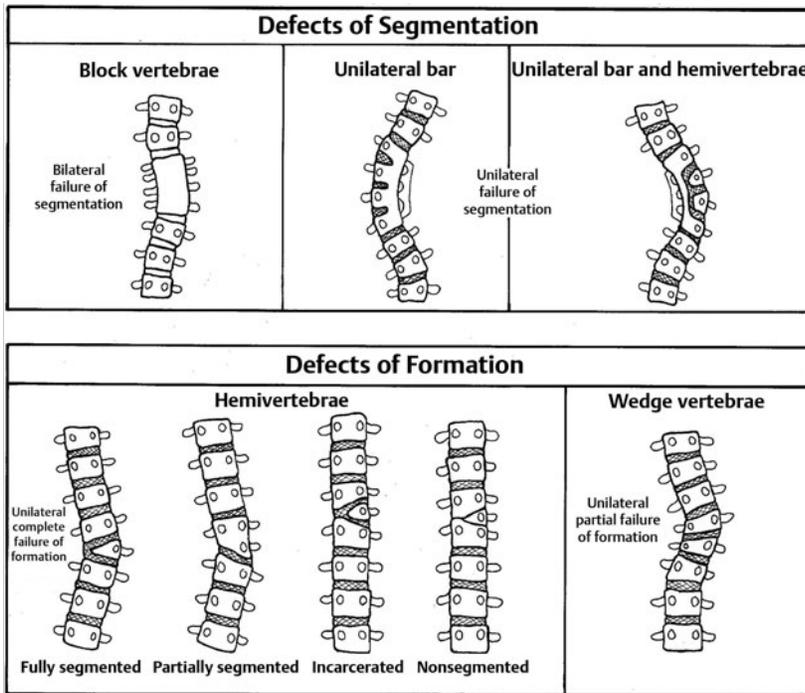


Fig. 29.1 Schematic drawings representing defects of segmentation and formation.

vertebral body segmentation anomalies are thought to arise as a result of disordered ossification.^{17,35,39}

Recent work has described a smaller, significant group of complex congenital vertebral anomalies that result in either craniocervical deformity and instability or congenital kyphoses (see box “Special Congenital Vertebral Anomalies” (p. 366)).^{35,36,39} These disorders include atlantoaxial hemivertebrae, congenital vertebral dislocation, segmental spinal dysgenesis, and medial spinal aplasia. Because it is unclear whether they can be explained by the traditional classification system, they are placed together under a separate heading. An atlantal hemiring is probably the most common cervical congenital vertebral anomaly seen by pediatric neurosurgeons.⁴⁰ Atlantal hemiring is defined as a bony discontinuity of the C1 ring in conjunction with the lateral displacement of the C1 lateral masses. It is frequently associated with occipital condyle abnormalities and absence of the transverse ligament, and it often leads to significant craniovertebral instability

Special Congenital Vertebral Anomalies

- Congenital vertebral dislocation
 - Involved vertebrae malformed
 - Superior vertebrae: elongated posterior elements with abnormally large spinal canal, bifid or incomplete laminae
 - Inferior vertebrae: misshapen, may be either smaller or larger than normal, posterior elements typically normal, spinal canal normal at this level
 - Spinal cord: intact, displaced by bony elements
- Atlantal hemiring
 - Bony discontinuity of the C1 ring in conjunction with lateral displacement of the C1 lateral masses
 - Associated with occipital condyle abnormalities and absence of the transverse ligament
 - Often causes or leads to significant craniovertebral instability

- Segmental spinal dysgenesis
 - Multilevel congenital spinal stenosis, hourglass shape of spinal canal
 - Absent pedicles, neurocentral junctions and transverse processes at involved levels
 - Stenotic posterior osseous ring encircling the spinal cord, separated from the posterior vertebral cortex by fat-filled space
 - Absent nerve roots at level of the stenosis
 - Normal vertebrae above and below the malformation
 - Spinal cord present cranial and caudal to the malformation
 - Generally normal sensorimotor function or incomplete neurologic deficits
 - High incidence of associated anomalies: tethered spinal cord, equinovarus deformities, Klippel-Feil syndrome, crossover rib, renal agenesis or duplication, situs inversus, and tetralogy of Fallot
- Medial spinal aplasia
 - Segmental or suspended agenesis of between 3 and 11 thoracic and/or lumbar vertebrae without associated lumbosacral agenesis
 - Spinal cord agenesis caudal to the malformation
 - Complete congenital paraplegia below the level of malformation
 - Severe orthopedic deformities with “Buddha-like” posture

29.6 Natural History

Because of their relatively high incidence, a good deal of information is known about the natural history of scoliotic and kyphotic curves in patients with congenital vertebral anomalies. This information, coupled with knowledge of normal and abnormal spinal growth, can be used to make decisions about the need for and timing of surgical intervention.

The growth potential associated with hemivertebrae is determined by whether the defect is segmented, partially segmented, nonsegmented, or incarcerated.⁵ A *fully segmented hemivertebra* has normal disk spaces above and below the affected level and therefore has the potential for unopposed longitudinal growth. Isolated segmented hemivertebrae in the thoracic spine produce progressive curves with a deterioration rate of 1 to 2 degrees per year. If multiple hemivertebrae exist, the rate of deterioration can be as high as 5 degrees per year. Lumbosacral hemivertebrae produce oblique spinal deformities, resulting in marked pelvic obliqueness and significant compensatory curves in the thoracolumbar spine. A *partially segmented hemivertebra* is fused with one adjacent vertebra and has less potential to produce significant deformity. A *nonsegmented hemivertebra* is fused to the vertebrae above and below and therefore has no potential for growth. In these cases, progressive deformity does not occur, and treatment is rarely required. *Incarcerated hemivertebrae* are ovoid and have narrow growth plates with little growth potential. These hemivertebrae appear to be contained by the vertebrae above and below and are rarely associated with significant deformity.

Unilateral unsegmented bars produce a unilateral growth tether and scoliosis. Isolated unilateral unsegmented bars in the thoracic spine have the potential to deteriorate at a rate of 5 degrees per year and require treatment. If bilateral failure of segmentation occurs, producing block vertebrae, then the disk spaces are symmetrically fused and therefore have little potential for producing spine deformities.

Combination deformities involving failures of both vertebral formation and segmentation are often very complex and have an increased potential for causing significant spinal deformity. The combination of a unilateral unsegmented bar with one or more contralateral hemivertebrae, for example, can lead to a rapidly deteriorating thoracolumbar scoliosis that has the potential to progress at 5 to 10 degrees per year. In many cases, these combination anomalies are fused at the time of diagnosis to prevent severe, intractable deformities in the future.

More is known about the natural history of thoracolumbar scoliosis than any other congenital vertebral anomaly. According to McMaster and Ohtsuka,⁵ 75% of congenital thoracolumbar curves will progress during growth, and 50% will require treatment. The factors associated with an unfavorable prognosis included early age at curve onset, vertebral anomaly type, and deformity location. The risk for progressive deformity was increased in the presence of block vertebrae, wedge vertebrae, hemivertebrae, two unilateral hemivertebrae, a unilateral unsegmented bar, or, most severely, a unilateral unsegmented bar associated with a contralateral hemivertebra at the same level. With each of these anomalies, the rate of deterioration was least severe in the upper thoracic region and most severe in the thoracolumbar region.

Early experience with atlantal hemirings and associated conditions (condylar aplasia or dysplasia, absent transverse ligaments, and C2 anomalies) seems to suggest that many of these patients present with craniocervical instability that may progress over time. It is common to intervene with a craniocervical fusion by the age of 4 years because the biomechanical stability of the occipitocervical complex fails over time.

29.7 Clinical Presentation and Evaluation

The clinical presentation of congenital vertebral anomalies is highly variable. Although pain is the most frequent presenting symptom among adults, incidental findings, association with other syndromes, and abnormal posture (e.g., torticollis) are the major pathways to diagnosis among children. Nevertheless, pain, weakness, sensory change, autonomic disturbance, and spine deformity may all exist alone or in combination as the presenting complaints. Pain may predominate in the midline or in a radicular fashion. Weakness and sensory changes can also be in a radicular pattern or can be part of a myelopathic syndrome involving a specific vertebral level. Autonomic disturbances, including bowel and bladder changes, may occur, with urinary incontinence often presenting early. Many patients with congenital vertebral body anomalies have symmetric fusions or blocked vertebrae and so present with no obvious spinal deformity. Indeed, if the fusion exists at one or two levels only, these individuals may not even be aware of its existence until it is revealed by radiographs taken for unrelated causes. Other individuals, however, can have much more obvious deformities that are detected at any time from birth to early adulthood.

The physical examination of a patient with suspected congenital vertebral anomaly should begin with general observations. A low-lying hairline or web neck deformity typical of Klippel-Feil syndrome or abnormalities of the ears or palate associated with Goldenhar syndrome may be noticed. Dwarfism without evidence of mental retardation may suggest achondroplasia, spondyloepiphyseal dysplasia, or some other type of skeletal dysplasia. Careful examination of the skin on the back is important to detect cutaneous stigmata of spinal dysraphism, including hairy patches, skin discoloration, dimples, lipomas, hemangiomas, and other findings. Examination of the extremities may reveal ligamentous laxity associated with Ehlers-Danlos syndrome or Larsen syndrome. Physical findings in the feet may include high arches or cavus deformity, which are common in Friedreich ataxia. The association of both foot and spine deformities strongly suggests spinal dysraphism or a generalized neuromuscular disorder. Limb length discrepancy is present if the patient is standing and the pelvis is out of the horizontal plane; this can be quantified by placing blocks of variable thickness under the short leg until the pelvis is level. The patient, dressed comfortably in an examination gown, should be standing during the examination of the spine, which should proceed in a cranial to caudal direction in a systematic fashion. In general, a “physiologic” curve is convex to the right, whereas a “pathologic” curve is convex to the left. Tenderness over the spine should be sought, as well as a determination of the range of motion. A complete neurologic examination should also be performed, with particular emphasis on the cranial nerves, sensorimotor function, and deep tendon reflexes. The patient’s gait and station may provide subtle clues for the presence of lower extremity or truncal weakness.

29.7.1 Cervical Region

Torticollis, a twisting of the neck with the head tilted toward the involved muscle and the chin rotated toward the opposite

side (“cock robin” posture), is a common physical finding among children. Torticollis usually results from unilateral contraction and fibrosis of the sternocleidomastoid muscle; however, a retrospective study of 288 patients documented 53 (18.4%) with torticollis of nonmuscular causes.⁴¹ Although the majority of these had neurologic causes, almost a third were associated with vertebral anomalies. We routinely order plain cervical spine radiographs for children who present with torticollis to exclude vertebral anomalies before the initiation of physical therapy. In selected patients (e.g., those with vertebral anomalies or with severe deformity), thin-cut computed tomographic (CT) scans with two-dimensional reconstructions are ordered to further investigate the bony anatomy. Although torticollis usually responds to physical therapy, it must be carefully monitored because it may lead to severe, progressive problems.²⁰

Although the majority of congenital vertebral anomalies in children are asymptomatic, several anomalies should be considered when children present with neck pain or torticollis. Atlantal hemirings and congenital upper cervical anomalies are relatively frequent causes of torticollis in younger children. Cervical ribs, or anomalous ribs in the cervical region that point downward, vary in size from tiny ossicles to fully formed ribs. The ribs are usually asymptomatic unless they are large enough to compress nerves or vessels. Symptoms of venous compression include pain in the ulnar distribution, neck pain, and pain along the involved part of the brachial plexus.⁴² Another uncommon anomaly of the cervical spine is an absent pedicle, which is also largely asymptomatic. In 1990, a review of 55 patients found that 31 had cervical pain, most often after trauma. The typical radiographic triad is (1) the false appearance of an enlarged neural foramen caused by the absent pedicle, (2) a dorsally displaced ipsilateral articular mass and lamina with a dysplastic and reversed facet joint, and (3) a dysplastic ipsilateral transverse process.⁴³

29.7.2 Thoracolumbar Region

Except after trauma, neurologic dysfunction associated with spinal deformity of the thoracic level is usually insidious in onset and slow in progression. Most cases are associated with idiopathic or congenital spinal deformities, particularly kyphosis. The terms *kyphosis*, *lordosis*, and *scoliosis* refer to abnormally increased convexity in the curvature of the thoracic spine (lateral view), increased anterior concavity in the curvature of the cervical and lumbar spine (lateral view), and increased lateral deviation from the normally straight vertical line of the spine (posterior view), respectively.

Scoliosis of the thoracic and lumbar spine usually presents as a painless deformity and has commonly been found in school screening programs. Juvenile idiopathic scoliosis is defined as scoliosis detected in children between 3 and 10 years of age, and adolescent idiopathic scoliosis occurs between 10 and 18 years of age. The prevalence appears to decrease with increasing curvature: 2 to 3% for a curve magnitude of more than 10 degrees, 0.3 to 0.5% for a curve of more than 20 degrees, and 0.2 to 0.3% for a curve of more than 30 degrees. Progression appears to increase with increasing curvature.²⁶

The most sensitive diagnostic screening test for thoracolumbar spinal deformity is the forward-bending test. As the patient bends forward, the presence of a rib prominence or rotation is

highly suggestive of an underlying curve and can be measured with a horizontal inclinometer. A plumb line dropped from the center of the occiput to the gluteal cleft is able to detect any lateral deviation of the trunk. Scoliotic curves should be described by their apex and location, such as a right thoracic curve, left lumbar curve, and so on. Sagittal plane deformity should also be assessed, with an evaluation for excessive kyphosis or lordosis.

29.7.3 Lumbosacral Region

Segmentation anomalies are frequently found in the lumbar and sacral spine, but they rarely produce neurologic symptoms or signs in children. Hemiblock and wedge vertebrae contribute to scoliotic and kyphotic deformities.²⁰

Caudal agenesis encompasses numerous congenital malformations of the lumbosacral spine ranging from simple anal atresia to the absence of sacral, lumbar, and possibly thoracic vertebrae to the most severe segmentation failure of the lower extremities, sirenomelia.^{6,20} Children with caudal agenesis generally show normal cognitive development but are often paraplegic and seldom have associated treatable neurologic conditions, such as spinal stenosis and tethered cord syndrome. Caudal agenesis is discussed in more detail in a subsequent section.

29.8 Diagnostic Evaluation

29.8.1 Plain Radiographs and Curve Measurement

Plain radiographs form the foundation from which congenital vertebral anomalies are detected and treated. Cervical spine radiographs—including lateral, anteroposterior, and odontoid views—are mandatory when clinical evidence of cervical abnormalities is present. Careful interpretation, however, is paramount because normal vertebral growth and ossification may show variable patterns. In most patients with congenital vertebral anomalies of the cervical spine, dynamic flexion and extension studies should be performed to determine whether instability is present and to assess whether there is any change in the spinal canal width. If thoracolumbar scoliosis is suspected, then upright lateral and anteroposterior plain radiographs of the entire spine should be obtained for initial curve assessment. The Cobb method is recommended by the Scoliosis Research Society to measure the degree of spinal deformity. It is applicable to both idiopathic and congenital curves. To use the Cobb method, the examiner chooses the most tilted vertebrae above and below the apex of the curve. Lines are then drawn extending from the superior end plate of the top vertebra and the inferior end plate of the bottom vertebra. The angle formed when intersecting lines are drawn perpendicular to the above lines is the Cobb angle. Imaging the entire spine on a single radiograph allows an assessment of the magnitude of the curve, the pattern of vertebral anomalies, and the overall balance in sagittal and coronal planes. Equally important, it also allows an assessment of progressive decompensation and spinal balance.

29.8.2 Special Imaging

CT provides detailed information regarding the bony anatomy of congenital vertebral anomalies and is invaluable in the

treatment-planning phase of these disorders. Thin-cut (1 mm) axial CT scans with multiplanar computer reformatting in the sagittal and coronal planes (1 mm) give further insight into the anatomy of the anomaly, especially those in the cervical region. In addition, two-dimensional parasagittal reconstruction of the atlantoaxial region is critical when the use of C1–2 instrumentation is being contemplated for the treatment of instability at the craniocervical junction.^{44–46} With the advent of magnetic resonance (MR) imaging, the use of CT myelography for the evaluation of spinal cord anatomy has decreased precipitously. There are cases, however, where CT myelography may be preferable to MR imaging, such as when spinal instrumentation overlies the area of interest and produces significant MR imaging artifact.

MR imaging is the study of choice for evaluating spinal cord pathology. Congenital anomalies and acquired defects of the spinal cord can be identified at all spinal levels. Because of the inherent difficulty of detecting bony abnormalities with MR imaging, however, more than one imaging modality is often required. Plain radiographs, CT, and MR imaging all may be necessary to completely understand the anatomy of a given lesion. Because multiple spinal anomalies are commonly present in the individual patient, it is important to image the entire spine if any malformation is suspected.

In infants, ultrasound can be useful initially because monitoring devices do not need to be removed, transport is often not required, and patients can be closely observed during the examination. Furthermore, ionizing radiation is not involved, sedation is not required, and most institutions have the requisite equipment.⁴⁷ Among other things, ultrasound can provide information about posterior cystic lesions, Chiari malformation, syringomyelia, diastematomyelia, and the position of the conus.⁴⁸

29.9 Associated Anomalies

The physical proximity of the branchial arches, genitourinary system, viscera, and other tissues to the spinal column during development permits a localized teratogenic event to have an effect on multiple organ systems. The branchial arches arise from the intermediate mesoderm adjacent to the cervicothoracic somites. Thus, derangement of the somites or developing vertebrae can be associated with malformations of the structures that arise from the branchial arches. These structures include the outer ear, ossicles, semicircular canals, mandible, and parts of the maxilla and hyoid bone.^{49,50} Patients with Apert, Crouzon, or Treacher Collins syndrome, for example, tend to have craniocervical abnormalities or blocked cervical vertebrae and associated complex craniofacial anomalies. Those with Goldenhar syndrome often have cervicothoracic scoliosis associated with a hemifacial microsomia, with severe ear deformities frequently noted. The unilateral hypoplasia or absence of the ear in this syndrome is associated with mandibular hypoplasia, macrostomia, an ocular dermoid, and fused vertebrae or hemivertebrae, usually in the lower cervical and upper thoracic levels.⁵⁰

The pronephros also originates at the level of the lower cervical spine, and teratogenic factors at those levels can be associated with abnormal development of the genitourinary

system.⁵¹ Genitourinary anomalies, including unilateral kidney, ureteral obstruction, and duplication of the kidney, may occur in up to 25% of patients with congenital scoliosis.⁵²

Because of the close proximity of the developing spinal cord to the osseous structures in the spine, malformations of the central nervous system often coexist with congenital vertebral anomalies.⁵³ For example, Bradford and colleagues⁵⁴ found a 38% incidence of intraspinal anomalies in 42 patients with congenital scoliosis. There was also a 52% incidence of spinal cord abnormalities, with unilateral unsegmented bars and contralateral hemivertebrae. Other studies have shown that split-cord malformations are present in 5 to 20% of patients with congenital scoliosis.⁵⁵

29.10 Congenital Vertebral Anomaly Syndromes

29.10.1 Klippel-Feil Syndrome

Klippel-Feil syndrome is a relatively rare entity that is classically described as the clinical and radiographic triad of short neck, low posterior hairline, and cervical vertebral segmentation abnormalities. All three components of the triad occur in only about 50% of patients with the syndrome, leading to the alternative description of a Klippel-Feil “variant,” which encompasses a larger number of patients. Although the true incidence of Klippel-Feil syndrome or variant in the general population is unknown, it is estimated in reports to be 1 in 42,000 live births, or somewhere between 0.02 and 0.7% of the population.^{56–59}

Klippel-Feil syndrome is usually diagnosed in children after incidental radiographic studies. Gross spinal deformities, torticollis, scoliosis, or acute cervical symptoms occurring immediately after a relatively mild injury, however, may indicate the syndrome before imaging is obtained. In a minority of cases, Klippel-Feil syndrome presents as chronic cervical symptoms lasting months: progressive neck and upper extremity pain, paresthesia, or weakness; ataxia; vertigo; headaches; and vision problems.

Klippel-Feil syndrome is most often seen as a sporadic disorder, although autosomal-dominant and autosomal-recessive cases have been reported. Mutations in the *GDF6* and *GDF3* genes, both encoding bone and cartilage regulatory proteins, have been identified to cause the disease. Several different hypotheses have been proposed over the years to explain its origin and include primary vascular disruption, global fetal insult, primary neural tube abnormality, genetic predisposition, and failure of facet joint segmentation (see the previous section on etiology).^{29,32,34,60}

Abnormalities in virtually every organ system have been associated with Klippel-Feil syndrome. These include Chiari 1 malformation with or without syringohydromyelia and developmental anomalies of the head such as high-arch palate, lid ptosis, cleft palate, facial nerve palsies, Duane contracture of the lateral rectus muscle, and mixed-type hearing loss.^{61,62} Between 30 and 60% of patients with Klippel-Feil syndrome have genitourinary abnormalities, including unilateral kidney, malrotation of a normal kidney, ectopic kidney, horseshoe kidney, and renal pelvic and ureteral duplication, or genital anomalies.^{61,63,64} Unilateral renal agenesis, the most common anomaly among patients with Klippel-Feil syndrome, is 400 times more

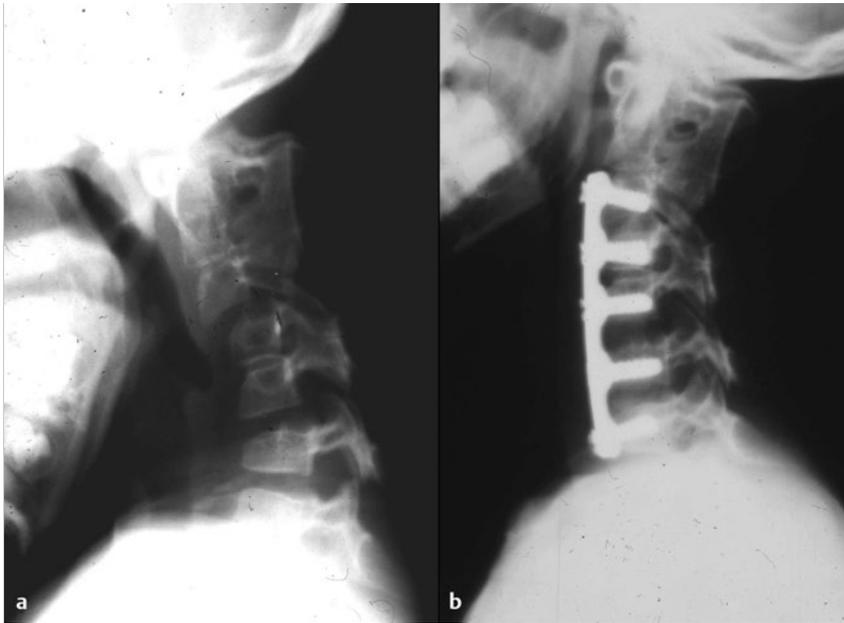


Fig. 29.2 A 9-year-old girl presented with Klippel-Feil syndrome. (a) Plain lateral cervical spine radiograph in flexion reveals significant subluxation at the C4–5 and C6–7 levels. (b) Postoperative lateral radiograph demonstrates multilevel anterior cervical discectomy and fusion with plating. The patient went on to have a successful fusion.

common in these patients than in the unaffected population. Among cardiovascular anomalies (which affect 4 to 5% of patients with Klippel-Feil syndrome), the most commonly reported are coarctation of the aorta, patent ductus arteriosus, mitral valve disease, and ventricular septal defects. Pulmonary anomalies include failure of lobe development, rib fusion, and ectopic lung secondary to a deformed trunk and rib cage. Syndactyly, elevation of the scapula (Sprengel deformity), and pterygium colli (webbing of the skin on the lateral side of the neck) have been reported.^{61,65} Hearing loss is common in patients with Klippel-Feil syndrome, occurring in up to 30%.⁶⁶ Accessory cervical ribs are found in 15% of patients with Klippel-Feil syndrome, whereas only 1% of individuals in the general population are similarly affected.⁶⁵

The Klippel-Feil syndrome involves segmentation anomalies of the spine, including fused vertebrae, hemivertebrae, occipitalization of the atlas, scoliosis, and spina bifida occulta (► Fig. 29.2). This places the cervical spinal cord at risk primarily because of the resulting biomechanical abnormalities. A common abnormality is congenital fusion of the second and third cervical vertebrae in conjunction with assimilation of the atlas.⁶⁷ Although this combination has been reported to result in atlantoaxial subluxation approximately 50% of the time,⁶⁸ our institutional experience suggests a much lower rate of instability (about 5%). Furthermore, congenital fusions over several spinal segments reduce the ability of the cervical spine to compensate for excessive forces in flexion, extension, rotation, and lateral bending, and stresses that might be tolerated by a patient who has a normal neck are not safe for one who has a cervical spine with limited mobility. Forces applied to the neck develop moments at each motion segment, and if only one or two motion segments exist where there should be eight, the force may exceed the strength of the restraining ligaments, leading to dislocation and injury to the spinal cord. In reported cases of patients with Klippel-Feil syndrome and spinal cord injury, the trauma is often minor or indirect, with the dislocation frequently self-reducing.^{69,70} Congenital spinal stenosis may

also be present in patients with Klippel-Feil syndrome, increasing the risk that even minor stress applied to the cervical spine can lead to neurologic injury.^{71,72} Anesthetic considerations for these patients are significant because children with Klippel-Feil syndrome are at high risk for spinal cord injury during laryngoscopy, intubation, and positioning.^{73,74}

After the original case description in 1912 by Klippel and Feil, Feil⁷⁵ developed a classification scheme in 1919 based on the location and extent of the vertebral anomaly. Type 1 lesions consist of massive fusion of the cervical vertebrae, sometimes extending to the upper thoracic spine, causing severe disability and an abnormal appearance. Type 2 lesions consist of only one or two fused vertebral segments and generally cause no symptoms in the first decades of life. Type 3 lesions are type 1 or type 2 lesions associated with distant anomalies of the thoracic or lumbar spine. In a study of 57 patients with Klippel-Feil syndrome, 40% were found to have type 1 lesions, 47% to have type 2 lesions, and 13% to have type 3 lesions.⁷⁶

The natural history of Klippel-Feil syndrome is incompletely understood. One of the most significant unanswered questions remains the fate of normal cervical levels adjacent to the naturally fused vertebral segments. In an attempt to answer this question, Theiss and colleagues⁷⁷ reported the long-term follow-up (over 10 years) of 32 patients with Klippel-Feil syndrome and congenital scoliosis. They discovered that only a small number of patients with Klippel-Feil syndrome and congenital scoliosis developed cervical symptoms, and they could not identify a fusion pattern that placed a patient at greater risk for such symptoms. In addition, the only factors that led to cervical symptoms were fusion at the cervicothoracic junction and congenital cervical stenosis. Nagib and colleagues^{73,78} also reviewed a group of patients with Klippel-Feil syndrome in an effort to identify those who were at higher risk for neurologic injury. The small number of patients, however, precluded meaningful recommendations. Further studies are needed to clarify the issue of when surgical fusion is necessary if an unstable, or potentially unstable, cervical segment is identified.



Fig. 29.3 A patient with C1 hemirings. (a) Coronal computed tomographic (CT) reconstruction showing displacement of the C1 lateral masses. (b) Sagittal CT reconstruction showing significant craniocervical displacement and canal narrowing. (c) Postoperative CT showing instrumentation from occiput to C4 and C5.

Several reports illustrate the importance of early, systematic studies and long-term follow-up.^{79,80} We routinely order cervical spine radiographs and perform neurologic examinations on a yearly basis for these patients.

29.10.2 Atlantal Hemiring Complex

Recent work has described a complex congenital vertebral anomaly of the craniocervical junction termed *atlantal hemirings*.⁴⁰ It is characterized by abnormal formation of the load-bearing structures of the craniocervical complex and includes lateral displacement of the lateral masses of the atlas, frequent absence of the transverse ligament, and variable amounts of dysplasia or aplasia of the occipital condyles and C2 lateral masses. It can be associated with Klippel-Feil syndrome. Patients typically present at an early age, sometimes before 1 year, with either torticollis or evidence of a cervical spine abnormality on routine radiographs such as chest radiographs. It is common for initial dynamic cervical spine radiographs to show evidence of significant craniocervical instability (► Fig. 29.3), and instability often increases as children age because of the greater stresses placed on the atlanto-occipital complex in older children lacking several major supporting craniocervical structures. Older patients (older than 3 or 4 years of age) who demonstrate significant instability may undergo fusion procedures shortly after presentation, whereas younger patients may be managed with a hard cervical collar and monitored with serial dynamic cervical spine radiographs until it is appropriate to proceed with surgical stabilization.

29.10.3 Osteochondrodysplasias, Collagenopathies, and Mucopolysaccharidoses

These disorders comprise a large number of syndromes that are associated with abnormal bony structure or metabolism. Common syndromes causing vertebral dysgenesis are listed in ► Table 29.1. They are mentioned in this chapter because abnormal

Table 29.1 Common syndromes associated with vertebral anomalies

Disorder	Type	Mutation
Osteochondrodysplasias		
Achondroplasia		<i>FGR3</i> mutation
Langer-Giedion syndrome		Chromosome 8 deletion
Chondrodysplasia punctata		<i>PEX7</i> , <i>GNPAT</i> , <i>AGPS</i>
Diastrophic dysplasia		<i>SLC26A2</i> mutation
Collagenopathies		
Spondyloepiphyseal dysplasia	2 11	<i>COL11A1</i> , <i>COL11A2</i> , <i>COL2A1</i>
Kniest syndrome		
Osteogenesis imperfecta	I	<i>COL1</i>
Mucopolysaccharidoses		
Morquio syndrome	MPS 4	Galactose-6-sulfate sulfatase β-galactosidase
Hurler syndrome	MPS 1	alpha-L-iduronidase
Hunter syndrome	MPS 2	Iduronate-2-sulfatase
Abbreviation: MPS, mucopolysaccharidosis.		

bony architecture or weakness inherent in the bone may lead to the collapse of vertebral segments or overt spinal instability. They must be managed according to the principles that guide the care of all children with vertebral anomalies. A short discussion of a few common disorders is appropriate here.

Osteochondrodysplasias

Osteochondrodysplasias are diseases that result in abnormal formation of either bone or cartilage. Achondroplasia is the most prevalent form of chondrodysplasia and is extensively covered in the following chapter. Other osteochondrodysplasias include Langer-Giedion syndrome, chondrodysplasia punctata, and diastrophic dwarfism (► Fig. 29.4).

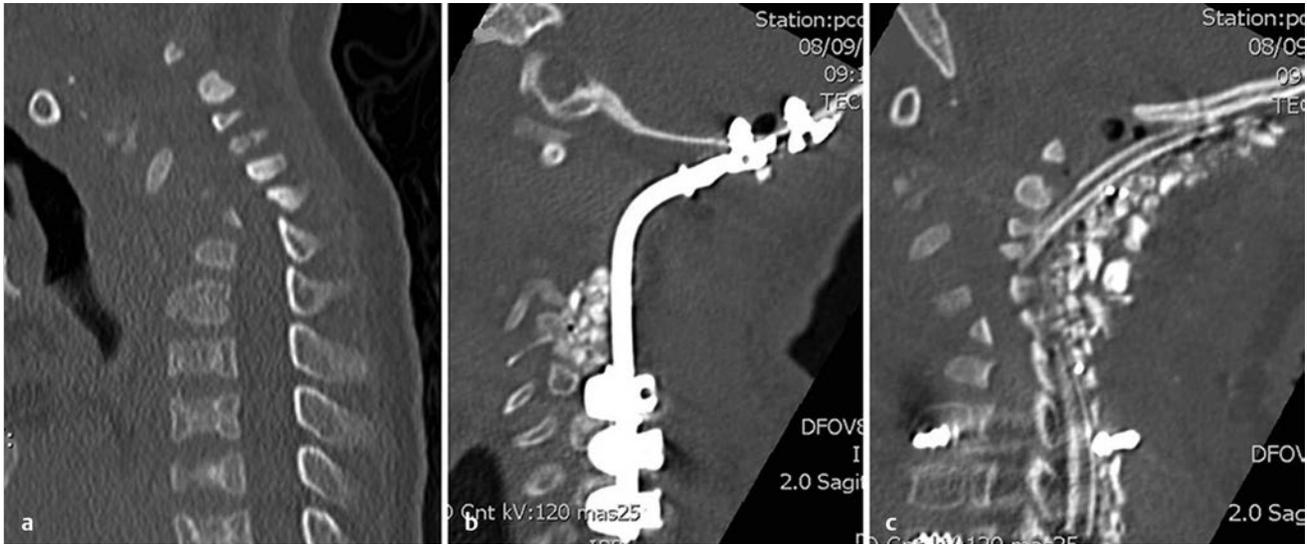


Fig. 29.4 A 4-year-old girl with chondrodysplasia punctata. (a) Sagittal computed tomographic (CT) scan showing significant bone loss in the upper cervical and midcervical spine. (b) Postoperative sagittal CT scan showing occipitocervical fusion instrumentation. (c) Midline sagittal CT scan showing postoperative fusion mass.

Collagenopathies

Collagenopathies are a group of disorders affecting connective tissue. They are caused by mutations in the *COL11A1*, *COL11A2*, and *COL2A1* genes. They include disorders such as spondyloepiphyseal dysplasia (SED) congenita and Kniest syndrome. SED is characterized by congenital dwarfism, with a short trunk, scoliosis, and epiphyseal dysplasia in the long bones and vertebral bodies.^{81–84} In addition to flat vertebral bodies and other congenital vertebral anomalies, a hypoplastic dens or os odontoidum is present in nearly all patients with SED, leading to atlantoaxial instability in 35 to 60% of patients.⁸⁵ Because patients with SED and spinal instability have had poor neurologic outcomes after even minor traumatic injuries, most authors advocate prophylactic surgical fusion regardless of spinal cord symptoms in the setting of instability.^{85–87} In our experience, most patients with SED have required surgical fusion. Additional challenges when surgical intervention is being considered for these patients include their small size for age, reduced pulmonary function, and often extreme spinal deformity.

Mucopolysaccharidoses

Mucopolysaccharidoses are a group of metabolic disorders caused by the absence or malfunction of lysosomal enzymes needed to break down glycosaminoglycans. These include Morquio, Hunter, and Hurler syndromes. A hypoplastic or aplastic dens is common in Morquio syndrome, with varying degrees of atlantoaxial subluxation present. Atlantoaxial fusion is often necessary to manage the instability.

29.10.4 Larsen Syndrome

Larsen syndrome is a complex syndrome with genetic heterogeneity and both autosomal-dominant and autosomal-recessive patterns of inheritance.^{88,89} It is caused by a mutation in the *FLNB* (filamen B) gene. Often categorized under the diagnosis of

arthrogryposis multiplex, Larsen syndrome is characterized by multiple congenital joint dislocations, a flattened facies, club-foot deformities, and cleft palate.⁹⁰ Although not emphasized in early descriptions of the syndrome, abnormalities of the cervical spine—specifically kyphosis, coronal clefts of the vertebrae, subluxation of the vertebrae, and atlantoaxial instability—can be the most serious manifestations of the disease.^{91–96} There is little information in the literature regarding treatment outcomes in these patients. Most authors advocate operative stabilization to reverse or prevent neurologic deficits. In patients with cervical kyphosis, posterior cervical fusion with instrumentation has been reported to provide stability and the opportunity for gradual correction of the deformity by continued anterior growth⁹² (► Fig. 29.5). If a severe kyphotic deformity is present, however, combined anterior and posterior stabilization procedures may be indicated.

29.10.5 Segmental Spinal Dysgenesis

Segmental spinal dysgenesis is a malformation resulting from an embryonic segmental malformation or focal injury to the developing spine in utero. Affected children are identified at birth by a sharply angled kyphotic deformity (thoracolumbar junction), anomalies of the lower extremities (usually equinovarus deformities of the feet and flexion contractures of the hips and knees), hyperreflexia of the lower extremities, and bladder dysfunction (usually manifesting as a low-pressure, dribbling urine stream).³⁷ There is marked focal hypoplasia of the vertebral column, typically at the thoracolumbar junction. Imaging studies reveal a kyphotic deformity with hypoplasia or absence of one or more vertebral bodies (► Fig. 29.6). Below the segmented agenesis, the bony spinal canal, thecal sac, and spinal cord resume a normal appearance. Evaluation of the entire spinal column is essential because affected patients may have associated lipomas, dermal sinuses, or syringomyelia. Surgery to decompress the bony narrowing at the site of dysgenesis can lead to an

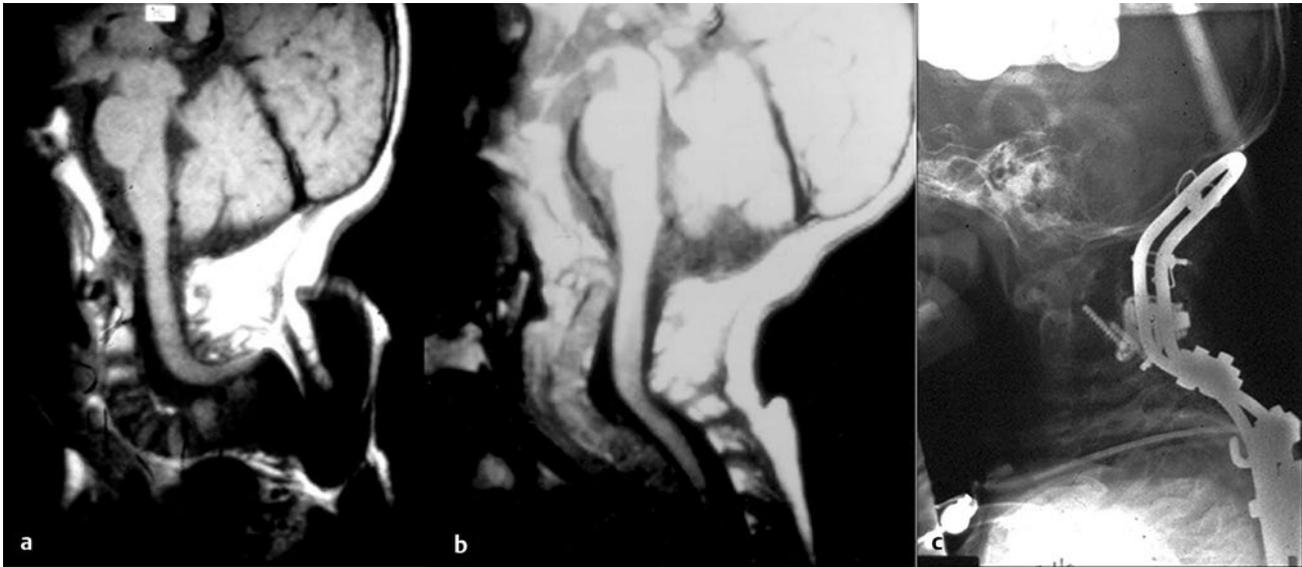


Fig. 29.5 T1-weighted magnetic resonance images of the midsagittal cervical spine (a) before traction and (b) after traction demonstrate significant reduction in an 8-year-old boy with severe progressive swan neck deformity due to Larsen syndrome. (c) Postoperative lateral radiograph demonstrates the instrumentation used in successful fusion.

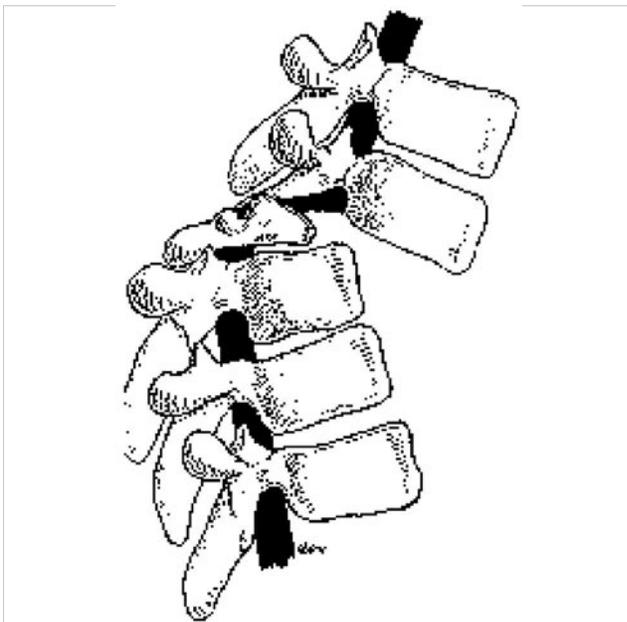


Fig. 29.6 Schematic drawing of segmental spinal dysgenesis with kyphosis.

improved neurologic outcome in some cases.³⁶ Early anterior and posterior arthrodesis is recommended for patients who have segmental spinal dysgenesis because the progressive kyphosis that inevitably develops often results in neurologic deficits.^{16,36}

29.10.6 Caudal Agenesis

The syndrome of caudal agenesis comprises a spectrum of anomalies, including sirenomelia (fusion of the lower extremities),

absence of the most caudal vertebral bodies and spinal cord, anal atresia, malformed external genitalia, exstrophy of the bladder, renal aplasia or ectopia, and pulmonary hypoplasia with Potter facies.³⁷ The vertebral malformations range in severity from agenesis of the coccyx to complete absence of the sacral, lumbar, and possibly even lower thoracic vertebrae.⁶

For practical purposes, the terms *caudal agenesis*, *caudal regression*, and *sacral agenesis* are synonymous. The reported incidence of caudal agenesis is approximately 1 in 7,500 births, although the wide clinical spectrum of malformations seen and the variability in diagnostic criteria preclude a truly accurate estimate.²⁴ Multiple classification schemes have been proposed over the years to describe caudal agenesis,^{2,97,98} but the most complete and useful system is likely the one proposed by Pang.⁶ The syndrome seems to result from disturbances of the caudal mesoderm, including the caudal cell mass and cloaca, before the fourth week of gestation.²⁴ The insult presumably impairs the normal migrations of neurons, paraxial mesodermal cells (somites that form the vertebral bodies), and lateral mesoderm cells that form the lower digestive tract.⁹⁹ Although the specific insult is unknown, there is a strong association with maternal diabetes^{100–102} and a softer association with industrial areas.²⁴

Because the urogenital and gastrointestinal systems are closely related to the vertebral column during development, caudal agenesis is often found in association with multisystem malformation syndromes. The most important of these are OEIS deformities (omphalocele, cloacal exstrophy, imperforate anus, and spinal deformities), which occur in approximately 10% of cases, and VACTERL anomalies (vertebral anomalies, anorectal malformations, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies), which occur in another 10% of cases.⁶ In nonsyndromic caudal agenesis, vertebral, urogenital, and anorectal anomalies occur together in a rather consistent triad. Other anomalies that may occur alone or in

combination with sacral agenesis include Hirschsprung disease, anal stenosis, renal anomalies, ambiguous genitalia, salpingoovaginal anomalies, and fistulas.

The presence of progressive neurologic deficits in patients with sacral agenesis is well-known and has been emphasized by Pang and Hoffman.^{6,7} Spinal cord tethering may be associated with a thick filum terminale (65%), terminal myelocystocele (15%), terminal hydromyelia (10%), or lipomyelomeningocele (10%). It is recommended that all tethering spinal cord lesions associated with caudal agenesis be released when progressive neurologic deterioration occurs. The role for prophylactic tethered cord release in this setting, however, is less clear.

29.10.7 MURCS Association

A distinctive association of müllerian duct aplasia, renal agenesis or aplasia, and cervical and thoracic spine dysplasia is described as the MURCS association.¹⁰³ Most patients are female. It is theorized that the association occurs because of the intimate spatial relationship at 4 weeks of development (blastoma phase) between the lower cervical and upper thoracic spine somites and the pronephric duct (which later induces müllerian duct development). A teratogen would alter all three of these structures and their subsequent development. Duncan⁵¹ reported that among patients with MURCS association, 80% have involvement of two to four vertebrae, 88% have renal agenesis or ectopia, and 96% have uterine hypoplasia or aplasia. Although there are reports of families with siblings who have MURCS, most cases seem to be sporadic.

29.11 Treatment Options

A discussion concerning all the possible treatment options and techniques for congenital vertebral disorders from the subaxial spine to the coccyx is well beyond the scope of this chapter. Furthermore, it is difficult to compare various surgical strategies with any degree of statistical confidence because surgery is not commonly necessary for children with congenital vertebral anomalies. It is appropriate to stress certain treatment principles that guide the management of these complex and varied disorders. In many cases, both neurosurgeons and orthopedic spine specialists must work together to treat the condition in a multidisciplinary fashion.

With the exception of juvenile idiopathic scoliosis, most pediatric experience comes from children who have anomalies such as Klippel-Feil syndrome and achondroplasia and from children whose anomaly was discovered incidental to trauma. Conservative treatment is always the first strategy when there is no immediate threat of permanent neurologic injury because therapy, exercise, and bracing can provide significant benefit for many children with congenital anomalies of the spine. It is important to determine whether clinical instability exists. Clinical instability is classically defined as loss of the ability of the spine under physiologic loads to maintain its pattern of displacement so that there is no initial or additional neurologic deficit, no major deformity, and no incapacitating pain.¹⁰⁴ Indications for surgery include the following: (1) reduction and/or stabilization of significant spinal deformity, (2) treatment of instability, (3) protection of the neural elements, and (4) relief of medically intractable pain, although this problem is rare in children.^{27,105}

29.11.1 Cervical Lesions

There are no published guidelines regarding the point at which cervical deformities or instability must be corrected with surgery. Minor cervical deformities or intervertebral motion that is greater than normal may be well tolerated by patients over many years. In cases of congenital or acquired cervical kyphosis or gross craniocervical instability, on the other hand, surgical correction may be required. Operative strategies to protect the neural elements in congenital vertebral anomalies usually involve bony decompression and/or fusion to improve or maintain neurologic function and axial alignment. It has been demonstrated that halo bracing or other cervicothoracic orthoses are often not successful in the face of a progressive craniocervical deformity.⁶⁵ The rate of curve progression, neurologic symptoms, and pain are all important factors in the decision to proceed with surgery. The decision for intervention must be made with the entire clinical picture in mind.

In the past, most patients underwent Gardner-Wells tongs traction before surgical correction of their deformity. Recently, however, improvements in spinal instrumentation have led to the ability to correct the vast majority of craniocervical deformities intraoperatively with rigid screw fixation techniques (► Fig. 29.7), which include both posterior and anterior approaches to the craniocervical area. Considerable experience has been accumulated with these techniques in the last decade in pediatric patients with a high degree of success. When an operative procedure is being, it is important to keep in mind that the need for external halo fixation postoperatively is low, as is the need for graft extenders such as bone morphogenetic protein-2 (BMP-2). In addition, successful allograft fusions have become more common and can be considered. Of course, the most critical factor for success is always the surgeon's training and technique.^{44,68,106}

Patients who have skeletal dysplasia often present with instability of the upper cervical spine. The presence of significant instability with atlantoaxial translation of more than 5 mm or cord compression in the upper cervical spine usually requires fusion.²⁷ If the C1 posterior arch is missing or bifid, as commonly occurs in patients with SED, fusion may need to extend to the occiput. Otherwise, only the two levels comprising the unstable segment need to be fused. Treatment options include posterior bone and wire fusion with external halo orthosis or posterior fusion with instrumentation. As mentioned before, many of the available instrumentation procedures eliminate the need for an external halo orthosis, which is a significant factor when a potential surgical procedure is being considered.⁴⁴⁻⁴⁶

Subaxial cervical instability secondary to congenital vertebral anomalies is relatively common and is most often seen in relation to Klippel-Feil syndrome. In that circumstance, an unstable vertebral level is commonly next to block vertebrae. Although either an anterior or a posterior surgical approach can be used to achieve fusion, we have had excellent results in which an anterior approach was used with an interbody graft and instrumentation (► Fig. 29.8). An anterior approach is also required when congenital swan neck deformities are treated. In this case, the apex of the kyphosis can be resected to achieve satisfactory neural decompression and facilitate curve correction and fusion; however, a posterior fusion with instrumentation must often be added to the anterior procedure to achieve complete reduction and stabilization (► Fig. 29.9).



Fig. 29.7 A 6-year old girl with os odontoideum and skeletal dysplasia. (a) Sagittal computed tomographic (CT) scan showing the os odontoideum. (b) Postoperative CT scan showing occipital–cervical instrumentation. (c) Postoperative midline sagittal CT scan showing restoration of the canal diameter.

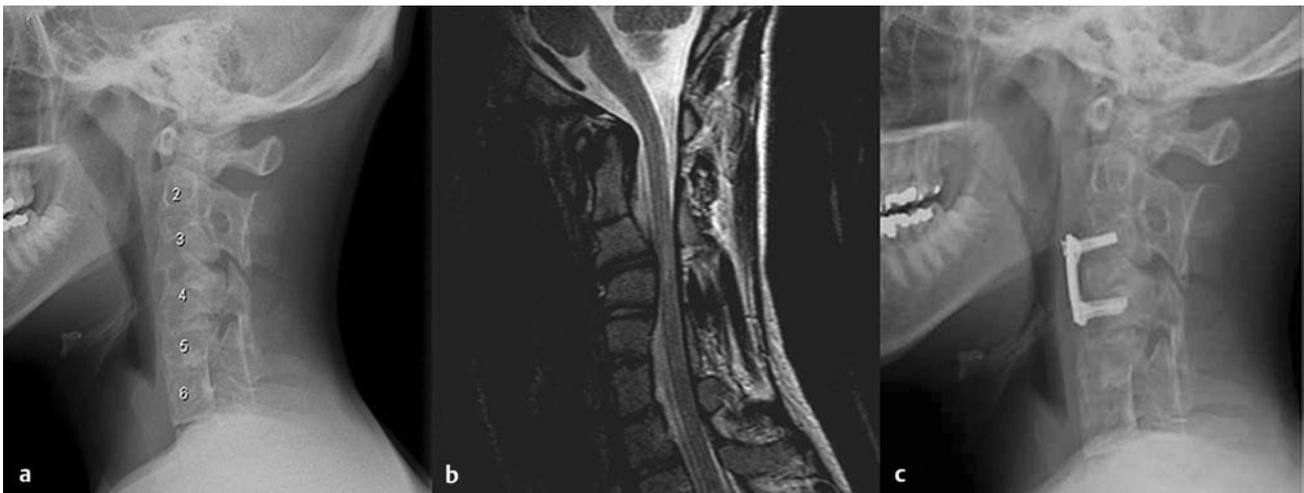


Fig. 29.8 (a) Radiograph of the lateral cervical spine of a patient with Klippel-Feil syndrome demonstrating multiple fused cervical vertebrae. (b) Sagittal T2-weighted magnetic resonance image from the same patient shows spinal canal narrowing with cord compression and signal change at the C3–4 disk space. (c) Three-month postoperative lateral radiograph after an anterior cervical discectomy and fusion with plating reveals solid bony fusion.

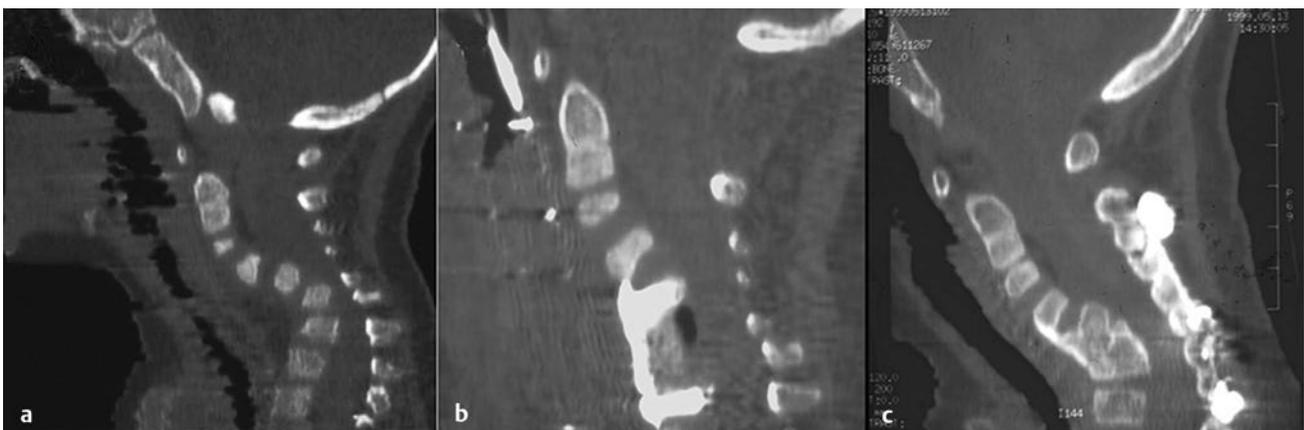


Fig. 29.9 An 18-month-old girl presented with severe swan neck deformity. (a) Preoperative midsagittal computed tomographic (CT) reconstruction demonstrates the severe nature of the kyphosis centered at C6. (b) Postoperative midsagittal CT reconstruction shows the appearance of the spinal column after anterior C6 corpectomy and fusion with plating. (c) Further stabilization was achieved with posterior fusion and instrumentation.

Part of the general treatment strategies for cervical congenital vertebral anomalies often involves discussions regarding activity restriction for the patient. Although there is no statistical evidence to suggest that uncomplicated stenosis of the cervical canal in a person with a stable spine predisposes the person to a permanent neurologic injury, experience suggests that children with fused cervical vertebrae, with or without craniocervical anomalies, are at risk for injury to the cervical cord from relatively minor trauma.⁷⁹ In general, recommendations have been advanced to restrict participation in collision activities (including football, hockey, wrestling, and other contact sports) in people who have a documented episode of cervical cord neurapraxia associated with unstable ligaments, disk disease with cord compression, significant degenerative changes, radiographic evidence of a cord defect or swelling, neurologic symptoms lasting more than 36 hours, and more than one recurrence.¹⁰⁷

29.11.2 Thoracolumbar Lesions

The goals for the treatment of thoracolumbar congenital vertebral anomalies are similar to those for the treatment of cervical lesions. The ultimate goal is to obtain a balanced spine that is as close to a complete correction as possible at the completion of growth. Because congenital scoliosis is a complex growth disturbance, treatment decisions and surgical timing may be difficult to determine. Each treatment strategy must be individualized based on the age of the patient at presentation, the type of vertebral anomaly, and the expected curve progression with growth. The treatment of adolescent or juvenile idiopathic scoliosis is not covered here.

The decision to surgically intervene in a congenital thoracolumbar vertebral anomaly requires regular assessment of the patient's growth and spinal curvature. This assessment can be achieved with serial radiographs. Yearly comparison of the radiographs is essential because growth within congenital vertebral anomalies may be unpredictable. Fundamentally, spinal growth occurs in areas of active end plates. Therefore, to control abnormal spinal curvature, sometimes the only option may be to retard a growing segment to maintain spinal balance. From an overall management point of view, it is often advisable to prevent a severe deformity rather than wait to correct one. It is often preferable to have a short, straight spine rather than wait for the completion of growth and attempt to correct a severe, decompensated curve later. A unilateral unsegmented bar with contralateral hemivertebrae, for example, is so predictably malignant that early anterior and posterior fusion is indicated upon recognition (► Fig. 29.10). In addition, experience with congenital vertebral dislocations seems to suggest that aggressive management with anterior and posterior approaches results in the highest rate of success.^{35,36,39} On the other hand, many simple curve patterns, such as an isolated hemivertebra, remain well compensated and do not require intervention (► Fig. 29.11).

Thoracolumbar scoliosis due to congenital vertebral anomalies may be managed by observation, bracing, or surgery. Observation is appropriate for small curves, balanced curves at skeletal maturity, and curves at low risk for further progression, such as those associated with block vertebrae. Infantile idiopathic scoliosis, for example, may resolve if significant trunk rotation is not present.²⁷ This can be determined by measuring an angle

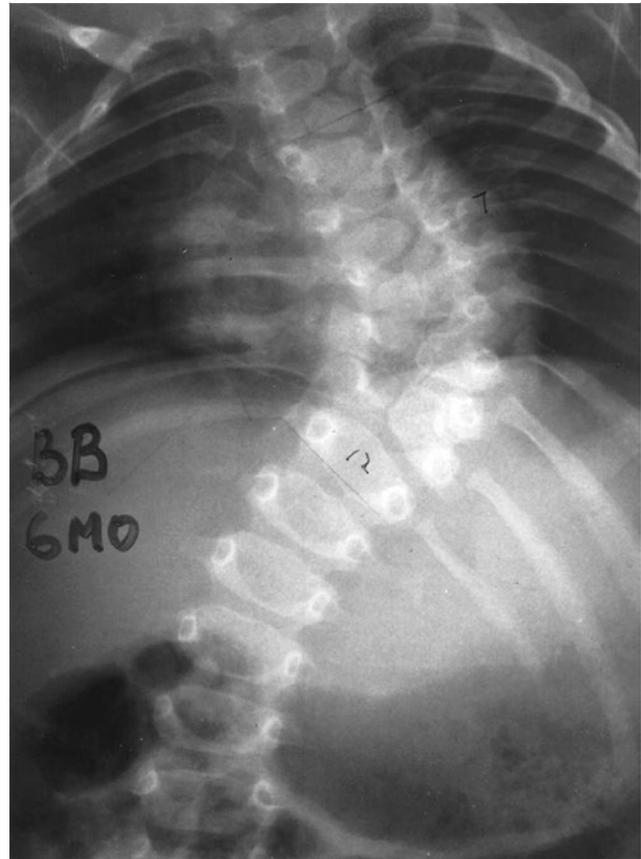


Fig. 29.10 Plain anteroposterior thoracic spine film in a 6-month-old child with unilateral failure of segmentation in association with multiple contralateral hemivertebrae.

between the ribs of less than 20 degrees at the apex of the deformity. Approximately 25% of children with congenital scoliosis may be managed with observation alone.¹⁰⁵ Neither exercise nor electric stimulation has any proven value.²⁷

Bracing for congenital scoliosis is appropriate only in very specific circumstances. In the presence of a severe growth imbalance, a brace will never control curve progression. The principal value of bracing is to control the secondary spinal curvature resulting from the primary congenital curve. Bracing can also be of value after surgical correction in maintaining spinal balance during the process of fusion maturation.

Accepted techniques for the surgical management of congenital thoracolumbar scoliosis are posterior fusion without instrumentation,^{108,109} posterior fusion with instrumentation,^{109,110} anterior fusion with instrumentation,¹¹¹⁻¹¹⁴ and convex anterior and posterior epiphyseodesis.¹¹⁵⁻¹¹⁷ Some authors have recommended posterior fusion in situ (without attempting correction) for any curve with documented progression of more than 10 degrees.²⁷ The advantages of posterior fusion alone are its relative simplicity, neurologic safety, short hospitalization, low blood loss, and well-established track record.¹¹⁸ The disadvantages include minimal ability to correct an established curve, the need for a postoperative orthosis, and the potential for bending of the fusion mass with growth. Furthermore, young patients undergoing posterior fusion for hemivertebrae may develop the so-called crankshaft phenomenon or progressive lordosis.²⁷



Fig. 29.11 Plain anteroposterior thoracic spine radiograph in an 18-month-old child with a balanced pattern of multiple hemivertebrae due to a hemimetameric shift. This pattern of multiple segmented hemivertebrae allows good sagittal balance to be maintained.

Posterior instrumentation may be added to posterior fusion when some degree of correction is desirable in addition to arresting the progression of the curve. The advantages of adding instrumentation include a gain of some degree of correction, a reduction in the pseudarthrosis rate, and less dependence on corrective postoperative bracing. The disadvantages include a higher risk for the neurologic complications associated with instrumentation and spinal distraction during correction.^{108,110,119,120} These risks can be reduced by obtaining MR images preoperatively and using intraoperative spinal cord monitoring or a wake-up test. It is recommended that coexisting intraspinal anomalies requiring surgical correction (e.g., tethered cord) be managed first, before the congenital scoliosis is corrected.

More recently, anterior approaches with instrumentation have been used to achieve correction and fusion in some patients.¹¹¹⁻¹¹⁴ Advantages of this approach include correction and rebalance of the trunk through a shorter fusion segment, thereby preserving motion segments.¹¹¹⁻¹¹³ Disadvantages include a higher rate of implant breakage¹¹¹ and complications inherent to an anterior approach to the thoracolumbar spine, including transient sympathetic disturbances.¹¹²

Convex growth arrest of the spine through an anterior and posterior epiphysiodesis is a management alternative in younger children with a small amount of progressive scoliosis (► Fig. 29.12).^{109,110} Curve progression often results from unbalanced growth of the convex side of the anomaly. It follows that arresting this convex growth will stop further progression of the curve. If the concave side has a potential for growth, then some correction is expected from that side as well. An anterior hemiepiphysiodesis is another option for some patients, with its major advantage being that the spine may continue to grow, allowing gradual correction of the curve. The thoracic cavity and spine may be expected to have a better growth potential with this procedure than with an early circumferential fusion. The most common disadvantage is that the procedure may be only partially successful, slowing but not halting curve progression.

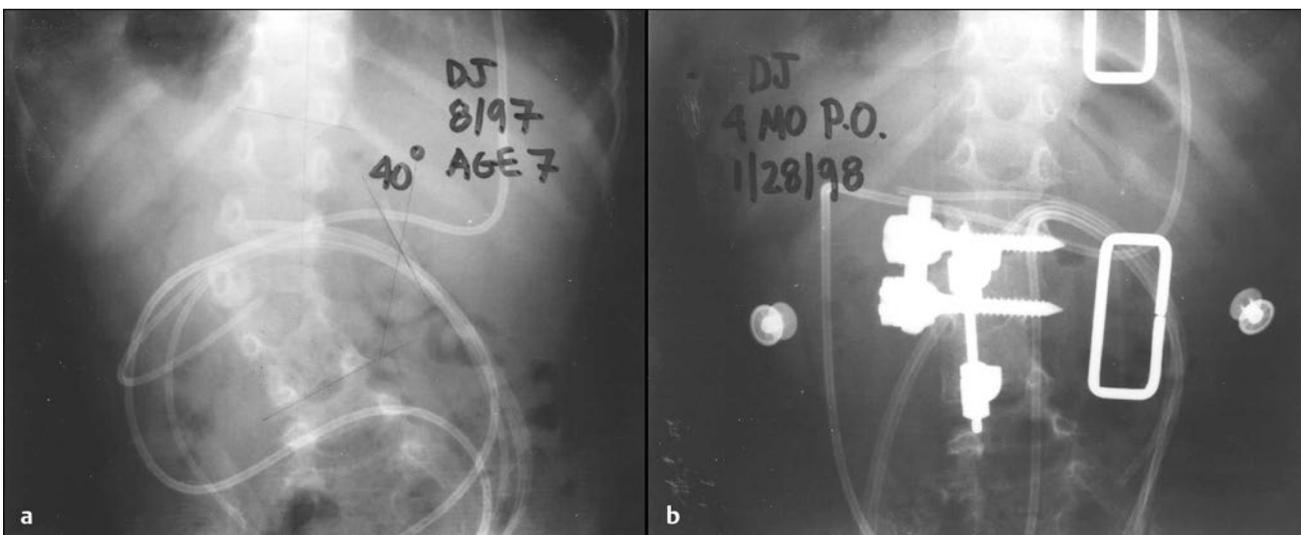


Fig. 29.12 (a) Plain anteroposterior film of the thoracolumbar spine in a 7-year-old boy with an isolated hemivertebra at L3 and hydrocephalus since birth. He developed a gradual loss of coronal balance with a progressive curve. (b) Thoracolumbar radiograph 4 months after an anteroposterior hemivertebrectomy shows that his coronal balance was restored.

Furthermore, the spine must be protected in a brace or cast while it is growing to avoid loss of fixation, which may lead to gradual rib deformity and a disproportionately small thorax.¹²¹

Excision of a hemivertebra may also be used to provide curve correction in certain cases.^{122,123} The principal indication of this procedure is the presence of a hemivertebra at the lumbosacral junction producing an oblique takeoff of the spine from the pelvis. Its main advantage is that immediate deformity correction and the restoration of spinal balance are achieved while fusion of a limited number of spinal segments is required. The disadvantages include the complexity of the procedure and an increased risk for neurologic injury. Significant amounts of correction are possible, and correction does not depend on unpredictable growth on the concave side of the curve.

Spondylolysis (alternatively isthmic spondylolisthesis), a failure of the neural arch manifesting as a defect in the pars interarticularis, is a congenital anomaly found throughout the spine that is often associated with other abnormalities, including spina bifida and dysplasia of the posterior processes.¹²⁴ It appears to be well tolerated, and it is most often medically managed in the adult. Nonoperative management usually suffices, but surgical intervention is occasionally required for those who are not successfully treated with reduction of activity and bracing. Recently, direct repair of the pars in the lumbar spine has been demonstrated to be a safe and effective modality to treat selected groups of patients with spondylolysis.¹²⁵ The advantage of direct pars repair over intertransverse fusion with or without segmental instrumentation is preservation of the anatomical integrity and motion of the affected segment. It is important, however, to distinguish relatively benign spondylolysis from spondylolisthesis with other, unstable causes, such as trauma.¹²⁶

29.12 Conclusion

Congenital vertebral anomalies are a dynamic, complex group of lesions occurring in the maturing spine. Intimate knowledge of their anatomy, biomechanics, and natural history is required to manage them effectively. A team approach is helpful in achieving management goals. Further effort is needed to better understand these complex issues.

Pearls

- Congenital vertebral anomalies are quite common. Many times, a combination of plain X-rays, CT, and MR imaging is necessary to establish a precise diagnosis.
- Once a diagnosis is made, important issues to address are the risk for neurologic injury, the risk for future deformity, and the presence or absence of spinal instability. In general, indications for surgery include the presence of a neurologic deficit or spinal instability or the prevention of future deformity.
- Modern surgical stabilization techniques, including rigid instrumentation, have allowed pediatric spine surgeons to manage more complex procedures with better outcomes.
- Much work remains to be done in this arena, including establishing the natural history of most disorders, the use of spine biologics in surgery, and the long-term outlook for children living with a spinal arthrodesis.

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30 Skeletal Syndromes

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Skeletal dysplasias comprise a group of disorders stemming from abnormal cartilage and bone formation, growth, and remodeling. There are more than 200 types of skeletal dysplasias, and various ways exist to characterize these disorders. They range from osteochondral dysplasias, which involve the whole skeleton, to the more limited dysostoses, which involve only a single group of bones. Skeletal dysplasias can also be categorized according to their pathogenesis as idiopathic osteolytic syndromes, primary chromosomal abnormalities, or primary metabolic abnormalities. For the purposes of this review, we concentrate on achondroplasia because it is the most common skeletal dysplasia that requires neurosurgical intervention. Other skeletal dysplasias that sometimes require neurosurgical intervention are addressed at the end of the chapter.

Achondroplasia is an autosomal-dominant disorder that affects the fibroblast growth factor receptor 3 (*FGFR3*) gene. This phenotype leads to disproportionately short stature with rhizomelic shortening of the extremities that results from the defective formation of endochondral bone.¹⁻³ Spontaneous mutations account for 70% of cases. Rare cases of homozygous achondroplasia are uniformly fatal primarily because of chest cavity restriction. Achondroplasia occurs in 1 in every 26,000 to 28,000 births, with an incidence of 0.03 to 0.05% of all live births.^{1,2,4} Bony compression of the neuraxis and respiratory failure are the primary sources of morbidity in achondroplasia.⁵⁻⁷ Most individuals with achondroplasia are of normal intelligence; however, their motor milestones may be delayed, partly because of the mechanical limitations of their short limbs and occasionally because of generalized hypotonia.⁸

Patients with achondroplasia present to neurosurgeons with three varying types of symptomatology: hydrocephalus, cervicomedullary compression, and spinal stenosis. Hydrocephalus and cervicomedullary compression present in infancy and childhood⁹ (► Table 30.1). Respiratory symptoms result from both mechanical obstruction and physical restriction. Upper small airway disease results in obstructive sleep apnea and manifests as snoring.¹⁰ Many infants compensate by hyperextending their necks during sleep to overcome this obstruction. However, extension of the neck exacerbates the small foramen magnum and cervicomedullary compression.¹¹ A smaller thoracic cavity can also result in restrictive symptoms, which may lead to respiratory compromise. This can be further compounded by gastroesophageal reflux, aspiration, and recurrent pneumonias. Spinal stenosis typically presents in young and middle adulthood. These patients present with neurogenic claudication, back pain, and occasionally urinary and bowel incontinence. We discuss further the work-up and management of patients who have achondroplasia with cervicomedullary compression and spinal stenosis.

30.1 Indications for Surgical Treatment

30.1.1 Cervicomedullary Compression

Patients with achondroplasia have neurologic manifestations in 35 to 47% of cases. They also have increased age-adjusted mortality rates at all ages, with the highest occurring in childhood. Foramen magnum stenosis is a common radiologic finding, but this does not always corroborate with the clinical symptoms. In a prospective evaluation, Pauli and colleagues studied 53 infants with achondroplasia.¹² More than 70% of the children had foramen magnum stenosis or associated craniocervical abnormalities on magnetic resonance (MR) imaging. However, only 14% of them developed clinical symptoms necessitating surgical decompression.¹² In an additional study, Reid and colleagues found evidence of foramen magnum stenosis in 60% of prospectively evaluated patients with achondroplasia, but only 35% demonstrated clinical symptoms of cervicomedullary compression.¹³

Foramen magnum stenosis results from defective endochondral bone growth and an abnormal fusion pattern of the posterior basal synchondrosis.^{4,14} The foramen magnum is formed by the exoccipital, supraoccipital, and basioccipital bones, which enlarge by endochondral ossification in cases of achondroplasia.¹⁵ The result is a small foramen magnum, short basicranium and clivus, shallow posterior fossa, horizontally oriented inferior occiput, abnormal odontoid process, stenotic jugular

Table 30.1 Cumulative percentage of affected patients by age in years

Complication	<1 y	<5 y	<10 y	<20 y	>20 y
Otitis media	60	93	96		
Ventilation tubes	16	68	78		
Tonsillectomy		25	33	37	39
Hearing loss		17	24	28	38
Speech delay		17	19	19	19
Orthodontics			3	22	48
Shunt	2	6	9	11	11
Apnea	8		13	16	16
Cervicomedullary compression	4		9	13	17
Cervical signs		4	7	8	15
Back pain		5		16	20
Spinal stenosis surgery			1	3	7

Source: Adapted from Hunter AGW, Banker A, Rogers JG, et al. Medical complications of achondroplasia: a multicenter patient review. *J Med Genet* 1998;35:705.

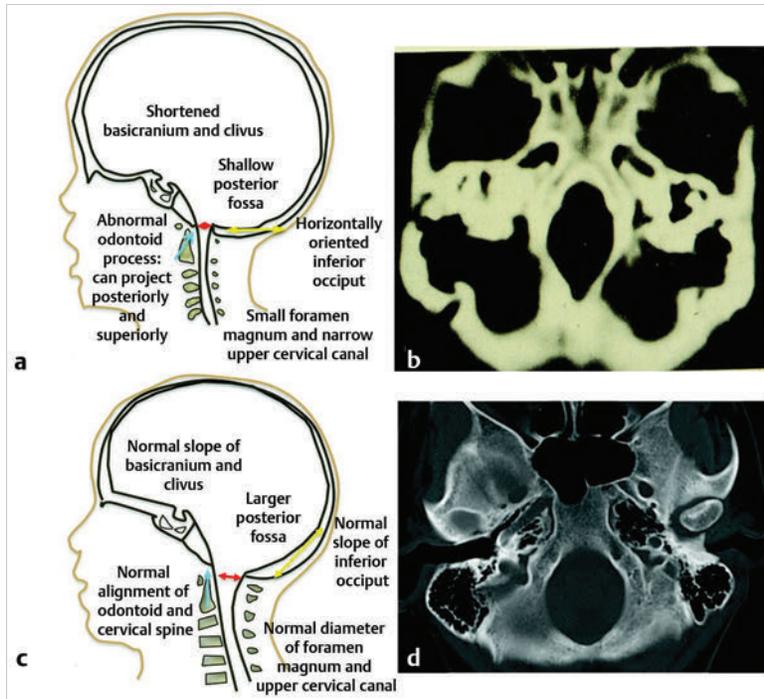


Fig. 30.1 Comparative foramen magnum anatomy in a patient with achondroplasia (a, b) and a normal person (c, d). Reduction in the sagittal and coronal dimensions of the foramen magnum leads to cervicomedullary compression (a). The cranial base is derived from endochondral ossification, which is not normal in achondroplasia. As a result, the base is stunted, shorter, and narrower than normal. The basioccipital bone is narrow and angulated, and the lateral and posterior parts have similarly abnormal characteristics that result in a diamond, triangular, or teardrop-shaped foramen magnum (b) in comparison with a normal skull base (d). The posterior fossa is small because the occipital bone is horizontally angled. This causes stenosis of the foramen magnum and cervical canal (a), which pushes the brainstem upward and applies pressure on the brainstem and upper cervical spinal cord.

foramina, and narrow upper cervical canal^{2,4,16} (► Fig. 30.1). These patients also have premature fusion and aberrant development of the two posterior synchondroses, which contribute to the stenosis and thickening of the foramen magnum rim.^{2,16} This can project into the brainstem and cervical canal. Further narrowing of the foramen magnum results from abnormal fusion of the posterior neural arch of the atlas with the posterior foramen magnum, as well as from dense fibrotic epidural bands found anterior to the posterior ring of the atlas.¹⁴ The odontoid process also can project posteriorly and superiorly, resulting in medullary compression.^{15,16}

Compression of the cervicomedullary junction can manifest as lower brainstem and high cervical spine compression leading to myelopathy, hydrocephalus, respiratory compromise, and sudden death. Young infants may have subtle findings but can have excessive hypotonia, poor head control, feeding or sleep difficulties, and apnea. Most patients with achondroplasia exhibit hypotonia during early infancy and can exhibit developmental delay in achieving motor milestones regardless of hydrocephalus.³ However, they typically catch up to normal children by the age of 2 to 3 years. Sudden death in infants with achondroplasia is the most feared complication of cervicomedullary compression. Hecht and colleagues reviewed a cohort of 781 individuals with achondroplasia and found a 7.5% risk for sudden death within the first year and a 2.5% risk for sudden death between 1 and 4 years of age.¹⁷ A retrospective analysis by Pauli and colleagues studied 13 patients with a sudden unexplained death or apnea. Of these patients, five had evidence of acute or chronic compression of the medulla and spinal cord at autopsy.¹⁸ Other postmortem studies have found similar cystic degenerative changes in the lower brainstem and syrinx formation of the upper cervical cord, concerning for chronic compression of the cervicomedullary junction.¹² Apnea may result from damage to respiratory control centers in the medulla,

compression of lower motor neurons that innervate the diaphragm and accessory muscles, and nonneurologic causes including upper airway obstruction, small thoracic cage, and mid-face hypoplasia.^{14,20–22}

There are two prevailing hypothesis for hydrocephalus in children with achondroplasia. The first attributes hydrocephalus to foramen magnum stenosis that leads to obstruction of the cerebrospinal fluid (CSF) outflow pathways, and the second attributes it to increased intracranial venous sinus pressure caused by compression at the jugular foramen. Yamada and colleagues favor the hypothesis of compression at the foramen magnum.¹⁵ However, patients have been noted to have relatively normal intracranial pressure (ICP) despite radiologic evidence of ventriculomegaly.¹⁶ Steinbok and colleagues found that raised intracranial venous pressure was secondary to stenosis of the jugular foramen, and occasionally of the jugular vein in the thoracic aperture.²² Treatments to consider include ventriculoperitoneal shunt and jugular foramen decompression, as these address the underlying etiology of the hydrocephalus. However, if the patient does not demonstrate signs of increased ICP, including headaches, lethargy, poor feeding, and irritability, therapy can be delayed as ventriculomegaly often abates with time.^{4,16}

Surgical intervention is based on signs or symptoms of neurologic dysfunction, not exclusively on radiologic imaging. Clinical signs such as apnea, lower cranial nerve palsies, hyperreflexia, sustained clonus, and weakness should be considered markers of cervicomedullary compression. Imaging findings that are suggestive of foramen magnum compression include intramedullary spinal cord changes on T2-weighted magnetic resonance (MR) imaging, lack of CSF flow anteriorly or posteriorly at the foramen magnum, and the presence of a syrinx (► Fig. 30.2). In a prospective analysis, Pauli and colleagues determined that lower limb hyperreflexia or clonus, central hypopnea on polysomnography, and foramen magnum

measurements lower than the mean for children with achondroplasia are the best signs and symptoms for predicting the need for surgical decompression.^{12,18}

30.1.2 Spinal Stenosis

The abnormal anatomical architecture of the achondroplastic spine contributes to both spinal cord and nerve root compression. The vertebral bodies have a classic mushroom shape on contrast myelograms secondary to hypertrophy of the superior and inferior articular facets.²³ Premature fusion of the centers of ossification of the vertebral bodies and the posterior neural arches results in laminae and pedicles that are short and thick. Posteriorly, the vertebral bodies assume a concave curvature. The consequence of this curvature can be improper projection

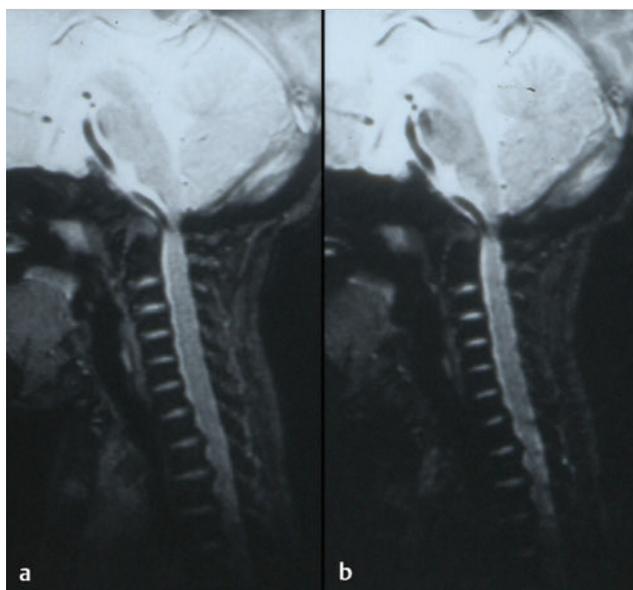


Fig. 30.2 (a) Sagittal T2-weighted magnetic resonance images showing a lack of cerebrospinal fluid flow anteriorly or posteriorly at the level of the foramen magnum. (b) The cervical canal also shows signs of congenital stenosis and a loss of normal lordosis.

of the inferior and superior ends into the spinal canal that further compromises the spinal subarachnoid space.²⁴ The overall scenario results in dramatic stenosis in every anatomical dimension of the spine (► Fig. 30.3).

Neurologic problems located below the foramen magnum often present later in adolescence. However, in one series of patients, symptomatic stenosis was seen 35% of the time in patients before the age of 15 years.²⁵ It is estimated that anywhere from 30 to 89% of patients with achondroplasia eventually experience symptoms associated with spinal stenosis. Children and adults typically present with multisegmental spinal stenosis involving the subaxial cervical or thoracolumbar spine. It is important to distinguish between the neurosurgical and the orthopedic characteristics for the management of the achondroplastic spine. Neurologic symptoms result from narrowing of the spinal canal due to a shortened pedicle length and small interpedicular distance. Orthopedic concerns result from patient issues such as physical limitations of the chest cavity and rotund abdomen, which tend to favor the formation of a progressive kyphosis.^{26,27} Some authors even discourage early ambulation and “sitting up” in these patients to minimize aggravation of their thoracolumbar kyphosis.⁸ In addition, hypotonia may prevent adequate protection of the skeletal structures in weight-bearing postures.⁹ Full-time bracing may be indicated if the kyphosis does not resolve by the age of 3 years, and if this fails to halt the progression of kyphosis, surgery can be indicated. Secondary instability can lead to worsening kyphosis or spinal deformity and is addressed in further detail below.

The evaluation of these patients in more advanced cases can reveal neurologic abnormalities, such as weakness of the lower extremities and hypoesthesia. Coexistent cervical and thoracic compression presents as spasticity and hyperreflexia of the lower extremities. Imaging should include both MR imaging and computed tomography (CT) for assessment and perioperative planning. MR imaging more frequently demonstrates disk pathology and any associated soft tissue hypertrophy (► Fig. 30.4). CT myelography has the advantage of revealing any regions of compression due to hypertrophy and providing information distal to the level of complete spinal block.

Urgent surgery is indicated for those patients who have neurologic impairments such as urinary incontinence or urgency, bowel incontinence, and worsening weakness that can

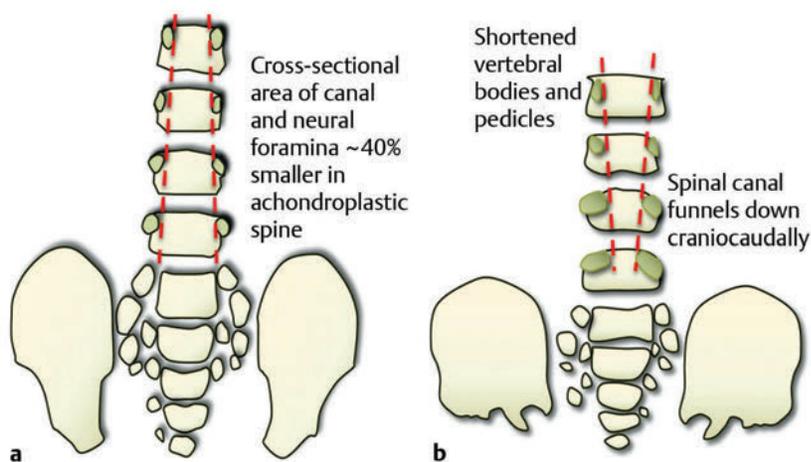


Fig. 30.3 Anatomical representation of a normal (a) and achondroplastic (b) spine. The anatomical architecture of the achondroplastic spine contributes to spinal cord and nerve compression, with hypertrophy of the superior and inferior articular facets, which show a classic mushroom shape on a computed tomographic myelogram. Premature fusion of the centers of ossification of the vertebral bodies and the posterior neural arches results in shortened and thickened laminae and pedicles. Additionally, the pedicles grow larger more caudally, and as a result, the spinal canal narrows in the lumbar region.



Fig. 30.4 Sagittal T2-weighted magnetic resonance (MR) image showing lumbar stenosis. MR imaging can more frequently demonstrate disk pathology and any associated soft-tissue hypertrophy. Posteriorly, the vertebral bodies assume a concave curvature that results in improper projection of the inferior and superior ends into the spinal canal.

be attributed to compression of the cord or cauda equina. Surgery should also be considered for patients with back pain secondary to stenosis, depending on how this affects their quality of life.²⁷ Decompressive laminectomies are indicated for patients whose ambulation is hindered by claudication and significant weakness at rest. Preoperative urologic testing should be performed as part of the work-up for a laminectomy, given the high rate of urinary incontinence that can result from surgery. This would include a urinalysis, urine culture, and urodynamic study to assess bladder compliance.

30.2 Surgical Treatment

30.2.1 Cervicomedullary Compression

Foramen magnum decompression is recommended early in the course of symptomatic cervicomedullary compression because

it has been shown to significantly improve outcome for these patients.^{7,28,29} An approach similar to the decompression of a Chari malformation can be utilized, which includes a suboccipital craniectomy and removal of the posterior arch of the atlas; however, the unique anatomy present in patients with achondroplasia must be taken into consideration during operative planning.

Patients are positioned prone on the operative table in slight flexion to minimize significant compression of the airway as well as to limit the subarachnoid space at the foramen magnum. Preoperative steroids are given to protect the spinal cord and brainstem from local trauma. The patients are followed with somatosensory evoked potentials (SSEPs) to assess for dorsal column injury. A midline suboccipital incision is made, and the posterior ligaments and paraspinal musculature are dissected subperiosteally to expose the occiput, spinous processes, and laminae of C1 and C2. The posterior arch of C1 is then removed with a high-speed drill. If there is significant compression further caudally, then the laminae of C2 must also be decompressed. The bone of the foramen magnum is thickened and oriented more horizontally than in typical pediatric patients and can indent the underlying dura. This angle can be assessed through preoperative imaging. The posterior rim of the foramen magnum should be gradually thinned and removed with small curets. There is typically a thick, fibrous band, or pannus, extending from the foramen magnum to C1 that should be left in place during the initial bony decompression to help protect the underlying dura. The most critical part of the bony decompression is removing the lip of the foramen magnum as this can be surrounded by the dura, making it difficult to remove without a durotomy.

Once the bony decompression is completed, the fibrous band can be removed. A transverse dural channel will indicate how restricted the dura was before decompression. The dura is often fused with this soft tissue band, and the annular sinus is commonly insinuated throughout the dura. If the band and dura are difficult to divide, then duraplasty should be performed in order to ensure removal of the compression. Duraplasty should also be performed if there is a persistent dural constriction after removal of the fibrous band. Intraoperative ultrasound should be used to confirm adequate cord pulsation and CSF flow. After duraplasty, a dural patch of pericranium, paraspinal fascia, or cadaveric dura is inserted to provide extra room at the foramen magnum. A watertight seal is essential as many of these patients have increased ICP and are at risk for the development of a CSF leak and possible pseudomeningocele. A ventriculostomy can be performed if there is preoperative concern for increased ICP or hydrocephalus that might complicate wound closure. Wound drains are not recommended as these can potentiate the development of a CSF fistula. Intraoperative SSEPs are critical throughout the procedure, and improvement will often be seen following decompression and restoration of CSF flow. Following the procedure, the surgeon should confirm movement in all four extremities before extubation. If there is a concern for a neurologic change, there may be damage to the underlying brainstem, and the patient should remain intubated until the respiratory drive and ability to ventilate are well established. Postoperatively, the patient should be monitored in an intensive care unit for any respiratory compromise or evidence of elevated ICP.

There are several points of difference between this procedure and a traditional decompression of the posterior fossa. The foramen magnum and posterior arch of C1 provide extensive constriction and pressure over the cervicomedullary junction. Introduction of even the smallest instrument can transmit significant pressure and compression to the underlying brainstem and spinal cord, and thus the surgeon should avoid placing any instruments, curets, or Kerrison rongeurs in this area. Patients with achondroplasia also have a relatively small posterior fossa with a small underlying brainstem and spinal cord, and therefore they do not need as large a decompression. The surgeon should have an appreciation for the actual size of the underlying neural elements and tailor the decompression to the appropriate size. The decompression should encompass the dorsal surface of the cervicomedullary junction along the lateral dimensions of the medulla in order to adequately decompress the stenosis at the level of the foramen magnum. This general area can be estimated by reviewing the preoperative MR imaging.

Patients with achondroplasia may also have significant engorgement of the veins lying below the ligamentum flavum both dorsally and laterally. These can be the source of significant bleeding, which must be rapidly controlled if they are entered. Air embolism can result from a tear in these venous structures, and the surgeon should ensure the patient is placed in the Trendelenburg position if this occurs and continue irrigation and packing of the area.

30.2.2 Spinal Stenosis

Patients with achondroplasia typically have a significant extent and severity of spinal stenosis. Historically poor operative results were obtained before the advent of CT and MR imaging as the degree of stenosis was often underappreciated.³⁰⁻³² Bulky instruments were used for decompression, and this frequently traumatized the underlying spinal cord and nerves. Postoperative instability was common, given the overly wide laminectomies performed for the size of the spinal canal.³²⁻³⁴ Review of the preoperative MR images and CT scans will show the degree of stenosis. If it is not clear, myelography can sometimes be used as an adjunct to show the level of stenosis, although it may not estimate the rostral to caudal length of spinal stenosis. The surgeon should be prepared with an operative plan that includes decompression of more than one or two segments above the level of the block and the same below.²⁵ Pediatric patients are more likely to require fusion in the future because the immature spinal canal has a greater propensity toward instability and deformation,³⁵ and thus we recommend a fusion procedure for any decompression of more than five levels and for any decompression crossing the thoracolumbar junction.

The patient should be in the prone position, and perioperative steroids should be given in a similar manner to that previously described. These patients should also be monitored for SSEP changes throughout the course of the procedure. A posterior midline incision is made, and dissection of the paraspinal musculature is carried out in a subperiosteal fashion to expose the spinous processes, laminae, and facet joints over the area of decompression. The laminae medial to the facet joints should be thinned with a high-speed drill or BoneScalpel (Misonix, Farmingdale, NY) to form a trough parallel to the longitudinal axis of the spinal column. The drill head should be pointed

toward the facet at approximately a 45-degree angle, which helps the surgeon maintain adequate control and avoid dural tears below. The groove is then thinned until the dura can be seen through the laminar mantle. This should be replicated on the opposite side for the length of the planned laminectomy. After the bone has been adequately thinned, a small dural patch can be inserted into the epidural space without significant compression on the spinal canal below. More recently, we have started utilizing the BoneScalpel (Misonix, Farmingdale, NY) which performs precise osteotomies through longitudinal ultrasonic oscillations. The device selectively impacts bone more than the surrounding soft tissue, and its blunt tip helps protect the underlying dura from trauma. We use this device to create bilateral troughs and can then remove the laminae en bloc without significant neural trauma. If the facet joints are violated throughout any part of this procedure, stabilization through spinal fusion becomes necessary. A retrospective analysis from our institution showed that children with achondroplasia and symptomatic stenosis were at high risk for progression to kyphotic deformity if more than five levels were removed through laminectomy.

Removal of the bony architecture in addition to dissection of the paraspinal musculature creates a deep void, especially at the lumbosacral junction. To avoid pseudomeningocele formation, a multilevel closure is performed to reapproximate the muscle masses and fill the dead space.³⁶ A paraspinal muscle encased in fascia is detached from the iliac spine and the lumbosacral laminae and reflected around its pedicle. The edge of the flap is brought down to the opposite lateral end of the laminae and is attached with resorbable sutures along the inferior part of the paraspinal muscles (► Fig. 30.5). The superior part of the muscle mass is then retracted over the first flap, thus completing the muscle closure and collapsing the void.

30.3 Treatment Alternatives

30.3.1 Cervicomedullary Compression

Traditionally, duraplasty has been offered to patients with achondroplasia for a more extensive decompression of the brainstem. However, in our institution, we have moved away from automatically performing a duraplasty unless adequate CSF flow is not restored following bony decompression and release of the fibrous band. As a result, the vast majority of our patients do not require duraplasty. Ultrasound is critical to demonstrate free movement of the brainstem and cerebellum.

30.3.2 Spinal Stenosis

Some investigators will argue that performing a wide decompression by undermining the facets and performing foraminotomies is necessary to adequately decompress the spinal cord and nerves.³⁵ However, in our experience, the lateral recesses in the patient with achondroplasia are relatively small, and we have not had a significant benefit in undermining the facets. Additionally, wider laminectomies are more destabilizing, and these patients go on to require more extensive surgeries in the future as a result. Spinal fusion should be considered up front for those patients undergoing extensive laminectomies of more than five levels.

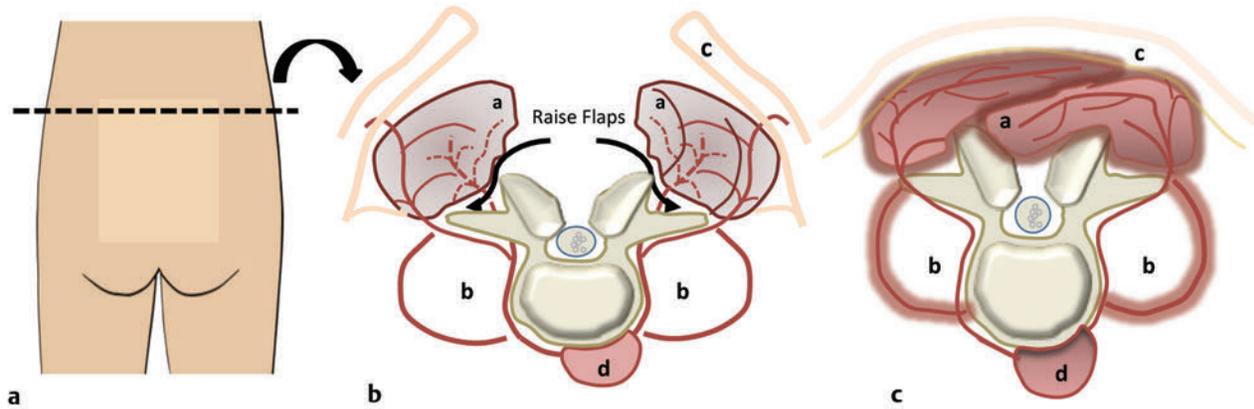


Fig. 30.5 Cross section of the lumbar spine (a) that depicts elevation of a paraspinous muscle flap (b). The paraspinous musculature (a) is released from any lateral attachments and reflected to cover the resultant laminectomy defect and any associated spinal hardware (c). Attaching the paraspinous muscles to each other is important to help fill the dead space over the dura. The psoas muscle (b), skin flap (c), and medial and lateral paraspinous perforator arteries originate from the posterior intercostal artery, which in turn originates from the aorta (d). Hydrocephalus and cervicomedullary compression present earlier, in younger patients, than spinal stenosis and back pain.

30.4 Prognostic Factors and Outcomes

30.4.1 Cervicomedullary Compression

Patients with symptomatic cervicomedullary compression usually show marked immediate improvement in their neurologic function after a successful decompression. In 2006, Bagley and colleagues reported on a series of 43 pediatric patients with symptomatic achondroplasia who underwent cervicomedullary decompression over an 11-year period. Most of their patients had sleep apnea or respiratory symptoms. All patients showed significant improvement of their respiratory symptoms after decompression.² There was no mortality, and the most common surgical morbidity was CSF leak in patients who had a durotomy. This was successfully managed by either reinforcement of the wound or CSF diversion in all cases. In another series, Aryanpur and colleagues reported on 14 pediatric patients with achondroplasia and cervicomedullary compression.²¹ Six of eight patients with apnea or cyanosis had total resolution of the issues after decompression. Nine of ten patients had improvement or resolution of their paresis, hyperreflexia, or hypertonia.²¹

A larger study, in which the 36-Item Short-Form Health Survey from the RAND Medical Outcomes Study was used, compared a total of 122 patients. A group of 66 patients with achondroplasia who were asymptomatic were compared with 56 patients who underwent decompression for symptomatic craniomedullary compression. The study showed that quality-of-life measures were not significantly different between the two groups, suggesting that despite undergoing surgery, patients with achondroplasia maintain a quality of life similar to that of patients who are followed with conservative management.³⁸

30.4.2 Spinal Stenosis

The treatment of spinal stenosis with surgical intervention has yielded mixed results.^{17,35} In the general population, multiple studies have concluded that time from onset of symptoms to laminectomy is a significant prognostic indicator of improvement.^{39,40} The importance of this prognostic factor has not fully been quantified in the prospective literature in regard to the pediatric population with achondroplasia. In 2011, Carlisle and colleagues described their experience with laminectomies in patients with achondroplasia at The Johns Hopkins University.³⁹ They showed that patients with a “time-to-surgery” interval of less than 6 months were seven times more likely to experience improvement in their walking distance and four times more likely to have Rankin Scale improvements than patients who had symptoms for more than 6 months.⁴² As with cervicomedullary decompression in patients with achondroplasia, it may be beneficial to recognize that earlier neurosurgical evaluation is needed because of the narrow therapeutic window before the development of permanent neurologic sequelae.

Spinal stenosis is more frequently encountered than cervicomedullary compression in patients with achondroplasia, and laminectomy provides adequate decompression for symptomatic patients. The morbidity associated with this procedure is higher in patients with achondroplasia than in the general population. In 1990, Uematsu reported a retrospective analysis of 67 patients over a 10-year period and found an improvement in symptoms in 70% of patients who underwent thoracolumbar decompression. Of the remaining patients, 22% experienced deterioration and 8% showed no symptomatic change. Intraoperatively, these patients were more likely to have durotomies (43%) because the dura is thinner in patients with chronic stenosis than in a normal adult population. Outcomes were quantified

with a functional rating scale and a comparison of functional assessments pre- and postoperatively. The best predictor for improvement following surgery was a shorter duration of symptoms before surgery. Urinary retention was the most common postoperative complication and developed in 38% of patients with spinal stenosis. Other complications included wound infection (13.5%) and pseudomeningocele that required operative repair (10%).⁴¹

Ain and colleagues published their series of postlaminectomy kyphosis in the thoracolumbar region in 10 patients with achondroplasia who underwent decompression for stenosis. They found that despite multilevel decompression, more than 50% of each medial facet was preserved in these patients that aided in maintaining spinal stability. However, all of the patients went on to develop kyphosis and subsequently underwent spinal fusions with instrumentation within 2.6 years of their original surgery. They recommended concurrent spinal fusion in patients undergoing at least five levels of laminectomy given the high risk for postlaminectomy thoracolumbar kyphosis.³⁵ A subsequent study also recommended spinal fusion in patients with a large decompression overlying a thoracolumbar kyphosis to avoid progressive postoperative deformity.⁴⁴

Baca and colleagues retrospectively reviewed a series of patients who underwent decompression for lumbar stenosis.⁴² Of the 18 patients studied, 9 had a fusion procedure at the time of their initial surgery and 9 did not. Only 2 patients from the fusion group required revision surgery during the follow-up period, whereas 7 of the patients who did not have fusion initially later required revision surgery (22% vs. 78%).⁴² Sciubba and colleagues reported their series of 44 patients and found that 72% of patients who underwent decompression also had fusion at the time of their surgery.⁴⁰ In the patients who underwent revision surgery, the thoracolumbar junction was at highest risk for junctional stenosis, and as a result, a fusion procedure is recommended when the area of decompression traverses the thoracolumbar junction.

30.5 Complications

The most common complication associated with craniocervical decompression is a CSF leak from the suboccipital incision or the site of a previously placed shunt. The reported CSF leak in the literature ranges from 15 to 25%.^{2,22} Foramen magnum decompression can be performed with an expected low rate of morbidity and can provide excellent clinical benefit.

Hydrocephalus and increased ICP are a concern in these patients as change in the bony anatomy predisposes them to higher-than-normal ICP and hydrocephalus. Following decompression, patients who had severe respiratory and neurologic disease can make significant developmental strides and experience resolution. One past series has shown an increased rate of shunt placement following cervicomedullary decompression.⁴³ The etiology behind increased ICP in patients with achondroplasia is unclear, but venous hypertension has been thought to play a role. However, our experience has shown that patients undergoing cervicomedullary decompression do not have a high rate of secondary shunt dependency following their procedure.⁴¹

Despite adequate decompression in spinal stenosis, restenosis may occur because of accelerated facet hypertrophy, bony overgrowth, and scarring. This may be due to instability in the spine or an exaggerated response to normal motion resulting from some interaction of the genetic components of the disease. Several series have shown that reoperation was necessary for achondroplastic spinal restenosis.³⁵ In one series, the reoperation rate was 4.3% for all patients with achondroplasia undergoing spinal decompression. The most common causes of recurrent stenosis were facet hypertrophy (75%), disk pathology (50%), bony overgrowth (37.5%), kyphosis (37.5%), spur formation (25%), and fusion construct (12.5%).⁴¹ Repeated surgery carried a higher risk for dural tear than the initial procedure. Destabilization due to a more expansive bony decompression that subsequently required fusion occurred in 50% of the cases. Despite the higher risk for morbidity and the possible need for fusion, 75% of the patients showed postoperative improvement in their strength.⁴³

30.6 Other Skeletal Dysplasias

Although in this chapter we have concentrated on the neurosurgical presentations associated with achondroplasia, there are other skeletal dysplasias that require neurosurgical evaluation. We briefly discuss both the congenital and genetic manifestations of the skeletal dysplasias commonly seen in the pediatric population (► Table 30.2).

Down syndrome is one of the more common congenital disorders arising from trisomy of chromosome 21. Cervical spine instability resulting from laxity of the ligaments surrounding the odontoid process is well documented.^{44–46} Radiologic instability identified from measurements of the atlantodental interval is seen in 10 to 30% of patients,^{44–47} but only approximately 1% of patients have symptomatic C1–C2 instability that warrants operative treatment. Osseous abnormalities including os odontoideum, odontoid hypoplasia, ossiculum terminale, and rotary atlantoaxial subluxation are also common and can contribute to instability.^{44,46} In addition, children with Down syndrome have occiput–C1 joint instability due to architectural changes in their bone that can be seen in 40 to 50% of patients with symptomatic craniovertebral abnormalities.^{44,45,50} Surgical treatment is recommended for any patient with more than 8 to 10 mm of subluxation at the occiput–C1 level.^{48,49,54}

Neurofibromatosis type 1 is an autosomal-dominant neurocutaneous syndrome that arises from a mutation in the *NF1* tumor suppressor gene located on chromosome 17. Among other findings, approximately 10 to 20% of children present with scoliosis.⁵¹ It has been suggested that this arises because of mesodermal dysplasia, endocrine disturbances, or in some cases osteomalacia arising from infiltration of bone by neurofibromas.⁵⁵ Dystrophic scoliosis may progress to kyphoscoliosis. Kyphoscoliosis involves dysplastic changes in the spine, with deformed vertebral bodies and an acute anteroposterior angulation resulting in neurologic impairment in some cases.

Osteogenesis imperfecta is a congenital disorder arising from a mutation in a gene for collagen turnover. It is associated with osteopenia and fragile bones that are susceptible to fracture. These patients have short stature and progressive skeletal

Table 30.2 Some of the more commonly presenting syndromes evaluated by neurosurgeons for surgical intervention

Skeletal dysplasia	Etiology	Physical findings	Neurologic findings
Achondroplasia	Autosomal-dominant missense mutation in <i>FGFR3</i>	<ul style="list-style-type: none"> • Short stature with rhizomelic shortening of the extremities • Macrocephaly with frontal bossing • Midface hypoplasia 	<ul style="list-style-type: none"> • Foramen magnum stenosis • Spinal canal stenosis • Hydrocephalus
Down syndrome	Trisomy of chromosome 21	<ul style="list-style-type: none"> • Low muscle tone • Flat facial features • Upward eye slant with abnormally shaped ears • Hyperflexibility • Hyperglossia 	<ul style="list-style-type: none"> • Cervical instability secondary to laxity of ligaments surrounding odontoid process • Craniovertebral abnormalities with occiput-to-C1 joint instability • Abnormalities of odontoid (os odontoideum, hypoplasia, ossiculum terminale, rotatory atlantoaxial subluxation)
Neurofibromatosis type 1	<i>NF1</i> tumor suppressor gene on chromosome 17	<ul style="list-style-type: none"> • Lisch nodules • Bone deformities • Café au lait spots and skin freckling • Neurofibromas • Short stature and large head size 	<ul style="list-style-type: none"> • Scoliosis from mesodermal dysplasia or endocrine disturbances, or osteomalacia from bony infiltration of neurofibromas • Neurofibromas • MSNPT
Osteogenesis imperfecta (types 1–4)	Mutation in <i>COL1A1</i> or <i>COL1A2</i> leading to decreased amount of collagen turnover	<ul style="list-style-type: none"> • Risk for bony fractures • Short stature • Progressive skeletal deformities 	<ul style="list-style-type: none"> • Kyphosis and scoliosis • Risk for compression fractures and vertebral body collapse • Basilar impression
Goldenhar syndrome (oculoauriculovertebral dysplasia)	Disruption in development of first and second branchial arches during the first 6 weeks of embryogenesis	<ul style="list-style-type: none"> • Craniofacial deformities (cleft lip) • Congenital heart defects • Hemifacial microsomia 	<ul style="list-style-type: none"> • Spinal anomalies (vertebral hypoplasia, failure of segmentation, failure of vertebral formation) leading to thoracolumbar kyphosis with segmentation anomalies • Spina bifida occulta • Sacral agenesis
Spondyloepiphyseal dysplasia	Several disorders arising from abnormal growth of spinal vertebrae and epiphyses	<ul style="list-style-type: none"> • Short-trunk dwarfism • Cleft palate • Coxa vara • Club foot • Myopia and hearing loss 	<ul style="list-style-type: none"> • Atlantoaxial instability due to odontoid hypoplasia or ligamentous laxity
Morquio syndrome (mucopolysaccharidosis type 4)	Autosomal-recessive lysosomal storage disease leading to inability to mobilize keratin sulfate	<ul style="list-style-type: none"> • Pectus carinatum • Thoracolumbar kyphosis and scoliosis • Genu valgum • Platyspondylia • Joint hypermobility 	<ul style="list-style-type: none"> • Atlantoaxial subluxation arising from odontoid dysplasia and ligamentous laxity
Larsen syndrome	Autosomal-dominant mutation in <i>FLNB</i> (filamin B)	<ul style="list-style-type: none"> • Hypermobility • Congenital dislocations • Brachycephaly • Cleft palate 	<ul style="list-style-type: none"> • Spinal deformities with flattened or hypoplastic vertebral bodies or posterior elements • Dysraphism and hemivertebrae • Absence of pedicles leading to dislocation

- Abbreviation: MSNPT, malignant peripheral nerve sheath tumor
- Note: More than 200 types of skeletal dysplasia have been described.

deformities. In some series, up to 80% of patients develop kyphosis and scoliosis that progress despite bracing.^{52,53} Patients with more severe cases (types 3 and 4) are too fragile to withstand any surgical intervention. These patients are also at risk for compression fractures and vertebral body collapse, as well as basilar impression.

Goldenhar syndrome, or oculoauriculovertebral dysplasia, is a heterogeneous disorder that is attributed to a disruption in development of the first and second branchial arches during the first 6 weeks of embryogenesis. Spinal anomalies include vertebral hypoplasia, failure of segmentation, and failure of vertebral formation that then lead to thoracolumbar kyphosis with segmentation anomalies. These patients can also present with block vertebrae, unilateral hemivertebrae, spina bifida occulta, butterfly vertebrae, and sacral agenesis.⁵⁵

Spondyloepiphyseal dysplasia encompasses several disorders arising from abnormal growth of the spinal vertebrae and epiphyses. These patients have short-trunk dwarfism, and severe spinal abnormalities are associated with the congenital form of the disorder. Patients develop atlantoaxial instability due to odontoid hypoplasia or ligamentous laxity that puts them at risk for spinal compression.⁵⁶

Morquio syndrome, or mucopolysaccharidosis (MPS) type 4, is an autosomal-recessive lysosomal storage disease characterized by an inability to metabolize keratan sulfate. These patients have short-trunk dwarfism with skeletal features that include pectus carinatum, thoracolumbar kyphosis, scoliosis, genu valgum, platyspondylia, flaring of the ribs, and joint hypermobility.⁵⁷ The most common spinal manifestation is atlantoaxial subluxation (42 to 90%) arising from odontoid dysplasia and ligamentous laxity that then leads to spinal cord compression.^{58,59}

Larsen syndrome is a rare congenital disorder of connective tissue that is associated with deformities of the spine: flattened or hypoplastic vertebral bodies or posterior elements, dysraphism, hemivertebrae, and wedged vertebrae.^{60,61} These patients also can develop progressive kyphosis and even anterior posterior dislocation due to an absence of pedicles. Cervical kyphosis is the most common deformity, occurring in approximately 12%, and can lead to quadriplegia and death.⁶⁰ Patients with Larsen syndrome are at risk for thoracic insufficiency syndrome secondary to the scoliosis that deforms the rib cage and limits adequate ventilation. There is a 40% rate of mortality due to respiratory complications.⁶² As a result, preoperative assessment of the patient's pulmonary function is essential and can include pulmonary function tests and bronchoscopy in addition to CT. Cervical spine kyphosis and subluxation should be treated with decompression and fusion before any correction of the scoliosis is undertaken given the concern for compression of the cervical spine. The progressive scoliosis can be addressed with one of the growth-sparing procedures that range from growing rods if there is minimal thoracic deformity to a VEPTR (vertical expandable prosthetic titanium rib) expansion thoracoplasty if there is significant thoracic deformity.⁶²

30.7 Conclusion

Skeletal dysplasias are a complex group of diseases affecting the bone or cartilage that originate from idiopathic, chromosomal, or metabolic abnormalities. Achondroplasia is one of the most common forms of skeletal dysplasia. It can affect the formation of the spinal canal and CSF drainage, and as a result, children with this condition are prone to the development of spinal stenosis, cervicomedullary compression, and hydrocephalus. Spinal stenosis is more frequently encountered as the patients age and can be addressed symptomatically with a decompression laminectomy. Given the high rates of progressive deformity, a fusion procedure is recommended for patients undergoing extensive laminectomies at the time of the decompressive procedure. Cervicomedullary decompression is a potentially life-saving procedure that^{54,55} removes pressure from the brainstem. Patients with achondroplasia in whom brainstem compression is a concern should undergo decompression in a timely manner because sudden death and developmental delays can result if the condition is left untreated. Hydrocephalus can also develop from skeletal stenosis of the CSF drainage pathways and jugular stenosis. Most patients with achondroplasia tolerate hydrocephalus well, but if there are concerns for increased ICP, a CSF diversion procedure should be considered.

Although the prevalence of achondroplasia in children in the population at large is relatively low, these children often have complex issues that require close monitoring and possible neurosurgical intervention. Other skeletal dysplasias also present with spinal instability or compression that can require neurosurgical intervention to address quality-of-life issues as well as significant medical concerns. Although there are inherent risks to any pediatric surgery, the potential benefit for these patients is significant.

Pearls

- Patients with achondroplasia should be managed by a multidisciplinary team. Regardless of the radiologic findings, surgery should not be offered unless the patient is symptomatic. However, careful neurologic follow-up is crucial, and surgery should be done at the first sign of neurologic compromise to avoid irreversible deficits.
- During cervicomedullary decompression, engorged veins lying below the ligamentum flavum both dorsally and laterally can be a source of significant bleeding.
- Dural tears can be commonly encountered during both cervicomedullary decompression and lumbar laminectomy. Urinary retention is commonly seen in the perioperative period and should be further investigated.
- Spinal fusion should be considered in pediatric patients with achondroplasia who are undergoing laminectomy, given the propensity of the vertebrae to develop deformity if left unfused.

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31 Syringomyelia and Hydromyelia

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Syringomyelia, or cystic cavitation of the spinal cord, is caused by various congenital, inflammatory, or traumatic problems of the brain and spine. Progressive syringomyelia causes neurologic deficits requiring surgical intervention. Although the cyst is often treated with direct drainage or shunting, treatment should ideally be directed at the etiology of the cyst. In this chapter, we review the incidence, pathophysiology, treatment options, and prognosis of syringomyelia as it relates to its various etiologies.

31.1 Definition

Spinal cord cavitation was first described in 1546 by Esteine in a treatise entitled *La Dissection du Corps Humain*.¹ The term *syringomyelia* was coined by D'Angers nearly 300 years later, in 1827.¹ In Greek mythology, Syrinx was “a nymph who was changed into a reed to save her from the amorous pursuit of Pan. From this reed, Pan then fashioned his musical pipes.”² Today, the term *syringomyelia* is used broadly to define a fluid-filled cavity (Greek *surinx*, “pipe”) within the parenchyma of the spinal cord (Greek *muelos*, “marrow”) that extends across more than one spinal segment. It is associated with a variety of pathologic conditions but is most frequently seen with hindbrain abnormalities such as the Chiari 1 malformation. It rarely causes death unless associated with bulbar symptoms.

Because syringomyelia comprises a family of disorders with different etiologies and potentially diverse pathophysiologic mechanisms, attempts have been made to classify it according to various criteria. Unfortunately, no classification scheme has satisfactorily illustrated all the major differences between the various forms of spinal cord cavitation. For instance, syringomyelia is divided into communicating and noncommunicating categories. A communicating syringomyelia consists of a cavity that communicates with the central canal and thus the fourth ventricle. Such a cavity is ordinarily surrounded by an ependymal lining and is located within the central canal, a condition also termed *hydromyelia* (► Fig. 31.1). In contrast, a syringomyelia is noncommunicating when the syrinx cavity does not involve the central canal. However, for the sake of simplicity in nomenclature, we use the term *syringomyelia* in all cases throughout this chapter.

31.2 Pathogenesis

The exact pathogenesis of syringomyelia is poorly understood. There is some evidence that in cases of direct compression of the spinal cord resulting from a mass, tight bony canal, tethering, or arachnoiditis, spinal cord edema may develop.^{3,4} Concomitantly, the patient may develop signs and symptoms of cord dysfunction that may return to normal or at least improve if the pathology is treated swiftly. Edema has been described as part of a “presyrinx” state and is well visualized on T2-weighted magnetic resonance (MR) imaging.^{3,4} When syringomyelia eventually develops, it can occur at any level, but it usually appears in close proximity to the area of known pathology and

extends from there. Nonetheless, most of the literature that attempts to dissect the pathophysiologic causes tends to argue a specific type of syringomyelia that results from hindbrain herniation. A discussion of these theories in detail is beyond the purpose of this chapter. Instead, readers are referred to the chapter on Chiari malformations and an excellent review of the subject,⁵ in which the hydrodynamic theory, the perivascular cerebrospinal fluid (CSF) dissection theory, the mechanical stress theory, and the intramedullary pulse pressure theory are described. Theories that relate more exclusively to other etiologies are discussed individually under the various etiologic subheadings.

31.3 Classification and Management of Syringomyelia Based on Etiology

31.3.1 Classification Scheme Based on Etiology

Conceptually, syringomyelia is a secondary abnormality caused by other spinal or cranial pathology. It is doubtful if primary syringomyelia actually exists, and it may be only a matter of time and improved technology before idiopathic syringomyelia can be explained and placed into previously undetected etiologic categories. One obvious example is that of the Chiari 0 abnormality, in which a pathophysiologic posterior fossa abnormality is assumed to be present (because the syrinx resolves with posterior fossa decompression) but which remains elusive anatomically (no posterior fossa abnormality is evident on diagnostic imaging). The anatomical problems currently recognized to cause syringomyelia include, but are not limited to, Chiari 1 and 2 malformations, congenital and acquired tethered spinal cord

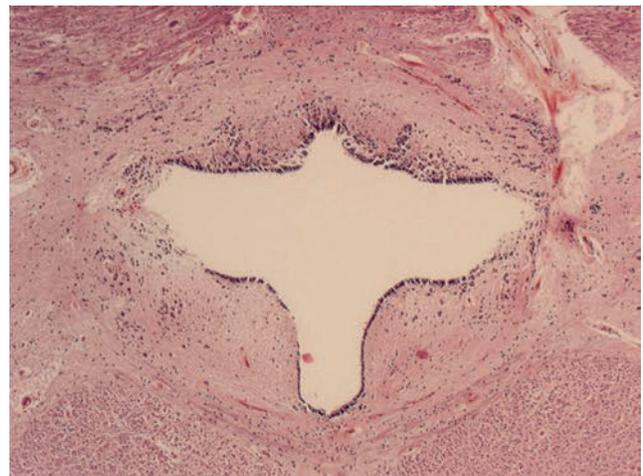


Fig. 31.1 Cross section of the cervical spinal cord showing a cystic cavity surrounded entirely by ependymal lining: “classic” hydromyelia.

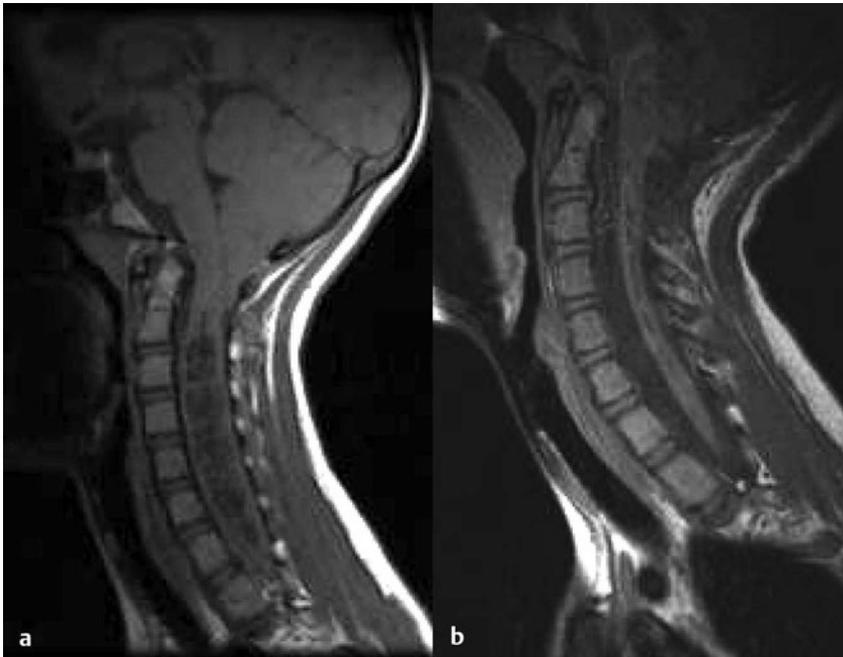


Fig. 31.2 (a) Sagittal magnetic resonance image of a 14-year-old girl with a Chiari 1 malformation and holocord syringomyelia. (b) Note the syrinx resolution after posterior fossa decompression.

(terminal syringomyelia), tumor, trauma, vascular malformation, degenerative stenosis and disk herniation, arachnoiditis, and infection. In this section, we classify syringomyelia based on these associated pathologies.

31.3.2 Management Scheme Based on Etiology

In general, the management of symptomatic syringomyelia is best approached by identifying and treating the associated condition thought to have caused the syrinx. The decision to treat syringomyelia surgically is straightforward when the patient is symptomatic, but treatment of the asymptomatic patient is more controversial. Small, asymptomatic syrinx cavities without any other obvious pathology may and often should be observed over time with serial imaging examinations. Conversely, an enlarging syrinx associated with progressive neurologic compromise merits timely surgical intervention. Difficulties arise in the large number of cases in which clinical or radiographic progression is not obvious, especially when no etiology is recognized (idiopathic syringomyelia) or when many potential etiologies coexist (e.g., spina bifida). Therefore, as with clinical presentation and pathophysiology, we discuss the general recommendations for surgical intervention according to etiology. The management algorithms presented after each section are guided by the literature but mainly reflect practice patterns garnered by the senior author's clinical experience.

31.3.3 Chiari 1

The Chiari 1 malformation consists of caudal displacement of the cerebellar tonsils into the upper cervical spinal canal approximately 5 mm below the plane of the foramen magnum. The vast majority of these malformations are congenital; however, acquired tonsillar herniation related to prolonged lumbar drainage or increased intracranial pressure has also been reported.

Although the occurrence of acquired hindbrain hernias only complicates the pathogenesis theories reported, it is reasonable to assume that syringomyelia in such cases is caused by a relative obstruction to the flow of CSF at the foramen magnum (► Fig. 31.2). Treatment almost uniformly consists of posterior fossa decompression. For data on the incidence, presentation, and treatment of syringomyelia associated with the Chiari 1 malformation, readers are referred to the relevant chapter in this textbook as well as the Chiari 1 Algorithm (► Fig. 31.3).

31.3.4 Chiari 2 (Spina Bifida)

The Chiari 2 malformation (or Arnold-Chiari malformation) occurs solely in patients with spina bifida and consists of caudal displacement of the cerebellar vermis, fourth ventricle, and brainstem.⁶ It is associated with hydrocephalus in more than 90% of patients and syringomyelia in 40 to 95%. The complicating factor in managing syringomyelia in patients with spina bifida is the fact that it is often difficult—if not impossible—to determine whether the syrinx is caused by hydrocephalus and shunt malfunction, Chiari 2, or a tethered spinal cord at the myelomeningocele repair site (► Fig. 31.4). However, it is increasingly apparent that regardless of the type of symptoms or imaging findings, the first treatment option to be considered should be cerebrospinal shunt revision (► Fig. 31.4). Readers are referred to the relevant chapter in this textbook and the Chiari 2 Algorithm (► Fig. 31.5 for more detailed information regarding this anomaly and its association with syringomyelia).

31.3.5 Chiari 0

Described in 1997, Chiari 0 defines idiopathic syringomyelia that improves in response to suboccipital decompression.⁷ Even though patients with Chiari 0 do not have tonsillar herniation on MR imaging, evidence suggests that Chiari 0 and Chiari 1 share clinical, radiographic, and genetic characteristics, as

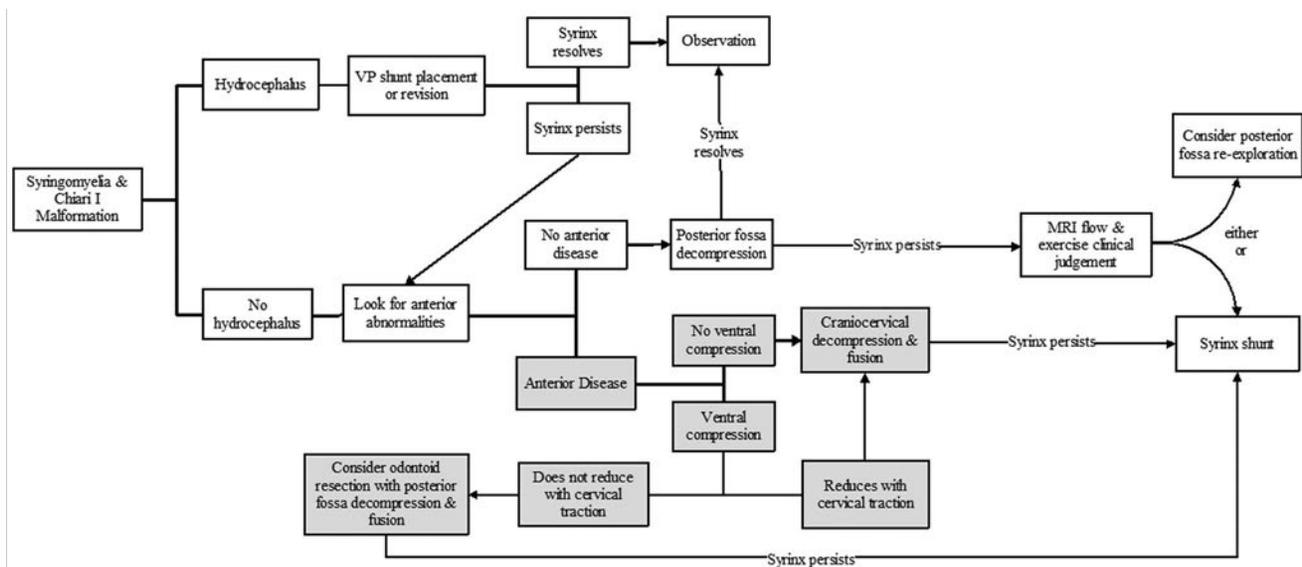


Fig. 31.3 Chiari I algorithm

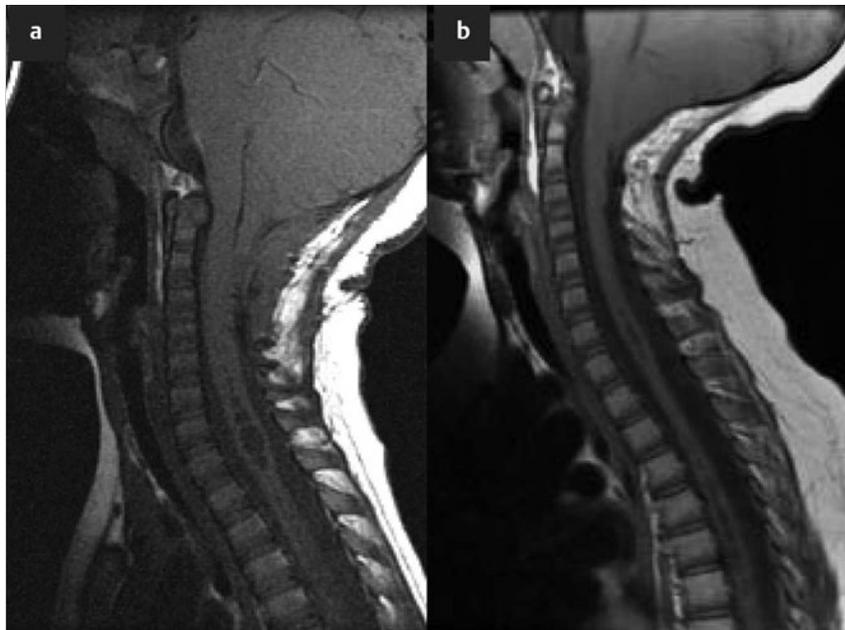


Fig. 31.4 (a) Sagittal magnetic resonance image of a patient with spina bifida showing a Chiari 2 malformation and syringomyelia. (b) The syrinx resolved after ventriculoperitoneal shunt revision.

detailed in the relevant chapter in this textbook.^{8,9} In general, however, the foramen magnum appears anatomically normal on imaging and intraoperative examination. This suggests that patients with Chiari 0 may have functional rather than anatomical obstructions at the foramen magnum,^{7,8,10} which one hopes can ultimately be identified with functional imaging modalities, such as cine flow MR imaging (see later section on imaging studies). It has further been hypothesized that Chiari 0 and Chiari 1 malformations are variants of the same disorder and have a common underlying pathophysiology. Regardless, our knowledge of Chiari 0 remains inadequate to determine the best treatment options (see Idiopathic and Chiari 0 Algorithm, ► Fig. 31.6). It is clear that some patients with idiopathic syringomyelia respond to posterior fossa decompression; 10 of 15

patients showed improved symptoms and signs after posterior fossa decompression in the largest series published to date.¹⁰ However, it is still unclear how these patients are different from other patients with idiopathic syringomyelia. Therefore, it is imperative to evaluate them thoroughly for other causative problems, such as tumors, arachnoiditis, and tethered cord, before any plan for posterior fossa decompression is made.

31.3.6 Tethered Cord (Terminal Syringomyelia)

Syringomyelia that occurs in the distal spinal cord, termed *terminal syringomyelia*, is often associated with spinal cord tethering. Tethered cord can be congenital or acquired. *Acquired*

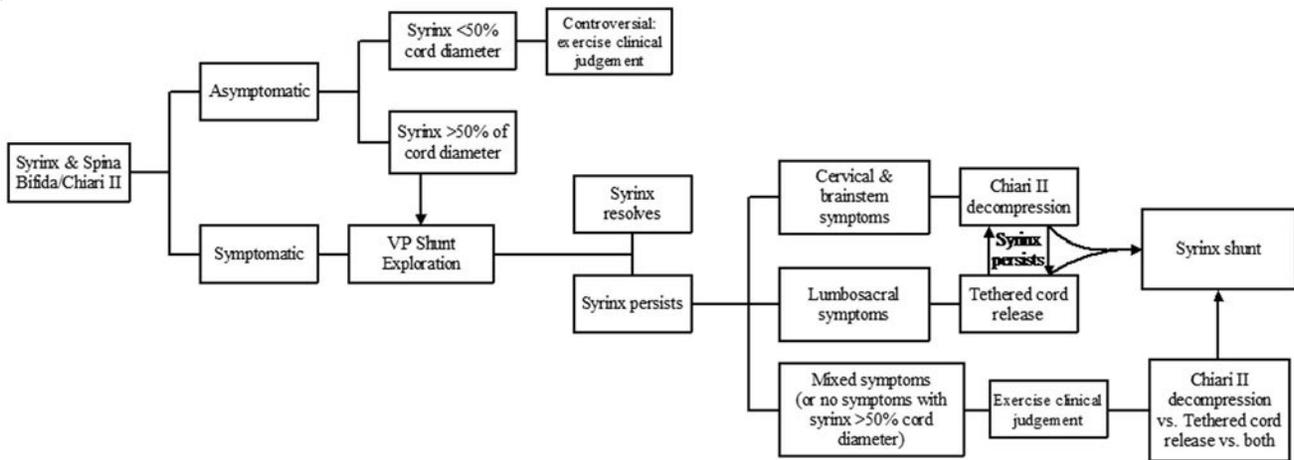


Fig. 31.5 Chiari II algorithm

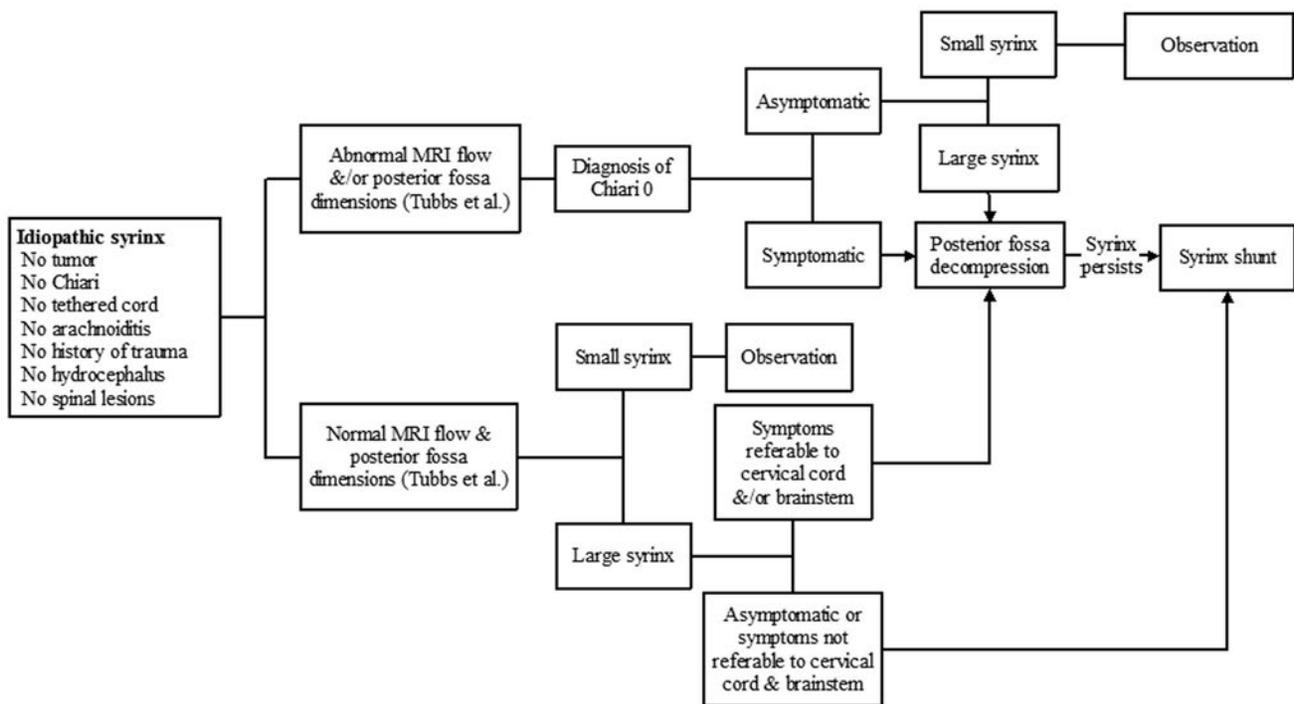


Fig. 31.6 Idiopathic and Chiari 0 algorithm

tethering usually occurs because of scarring, years after myelomeningocele repair. These patients are discussed in some detail in the earlier section on Chiari 2, and their cases are complicated by the fact that the Chiari 2 malformation and hydrocephalus may play a significant role in symptomatology and/or syrinx development. *Congenital tethered cord*, also known as spina bifida occulta, is associated with syringomyelia in 6 to 45% of cases (► Fig. 31.7). The spectrum of malformations that make up spina bifida occulta include tight filum terminale, split-cord malformation types 1 and 2, lipomyelomeningocele, dermal inclusion cyst with sinus tract, meningocele manqué, and neurenteric cyst.¹¹ Terminal syringomyelia associated with spina bifida occulta occurs in the distal third of the spinal cord¹²

(► Fig. 31.7). These patients do not have hydrocephalus, Chiari malformation, or other brain anomalies. The epicenter of the syrinx is usually located in close proximity to the tethering structure in the lumbosacral region. Patients with terminal syringomyelia often present with progressive bladder and lower extremity dysfunction. However, it is often impossible to distinguish between the symptoms associated with the syrinx and those associated with the cord tethering.¹² Releasing the tethered cord is essential in all patients with occult spinal dysraphism in order to prevent neurologic and urologic deficits, or the progression of already-existing deficits (see Congenital tethered cord algorithm ► Fig. 31.8).¹³ Older studies have suggested that when the associated syrinx is large in cross-section-

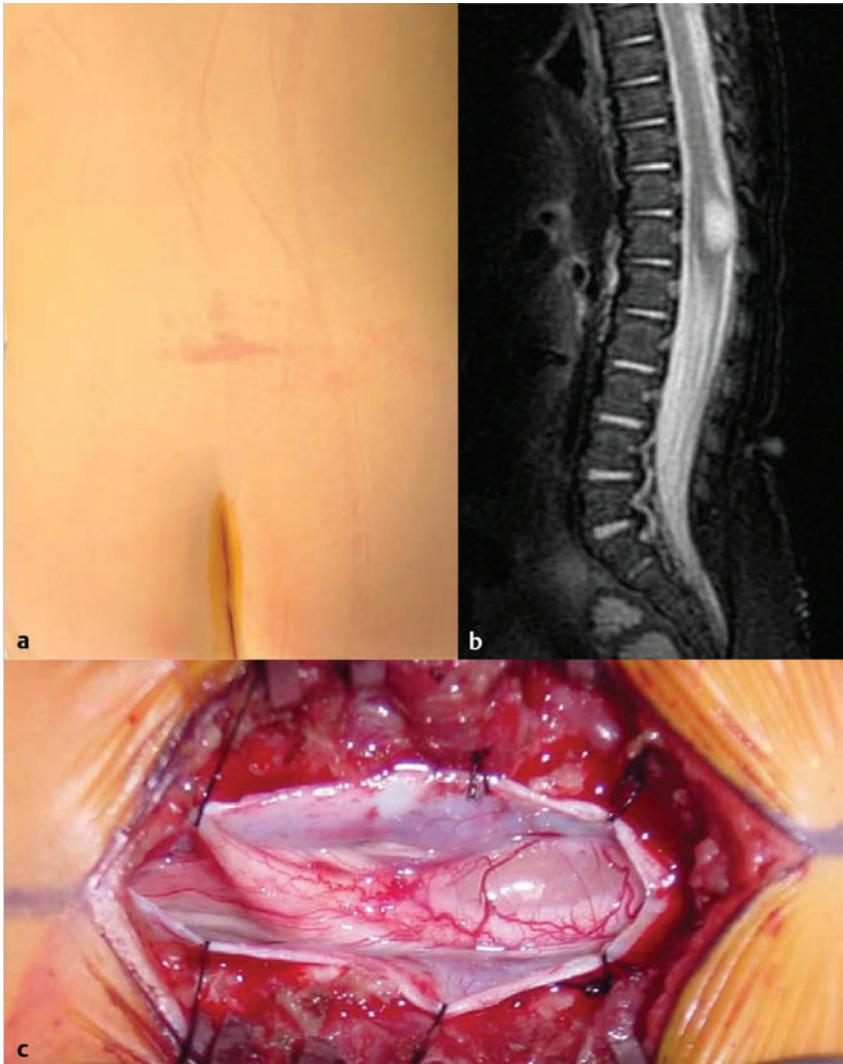


Fig. 31.7 (a) Terminal syrinx in a patient with a congenital tethered cord who presented with a lumbar hemangioma and (b) a conus in normal position. (c) Note the glistening surface of the thinned-out dorsal columns in the intraoperative photograph.

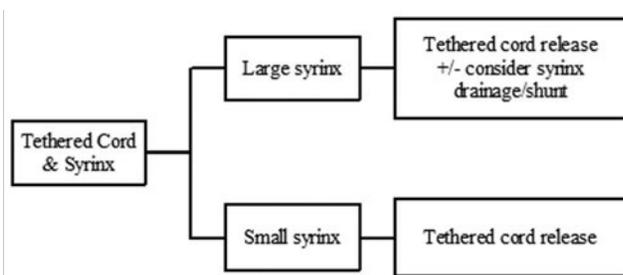


Fig. 31.8 Congenital tethered cord algorithm (terminal syringomyelia)

al diameter or extends for two or more vertebral levels in longitudinal dimension, it is preferable to place a shunt in addition to untethering.¹² However, more recent large studies have shown that terminal syringomyelia does indeed improve in response to untethering alone.^{14,15} Therefore, like syringomyelia due to foramen magnum pathology, syrinxes associated with tethered cord lesions appear to respond to correction of the underlying pathology, with a minority requiring direct shunting or drainage.

31.3.7 Arachnoiditis

Definition and Epidemiology

Spinal arachnoiditis can occur for a number of reasons, including infection (tuberculosis, bacterial or viral infection), chemical meningitis secondary to drugs and surgical interventions, and tumor (carcinomatous meningitis); even a familial form of spinal arachnoiditis has been described. Most commonly, however, it is associated with trauma. Imaging often reveals deformation of the spinal cord at the site of arachnoidal adhesions, blurring of a part of the syrinx wall (corresponding to the adhesive sites), flow void within the syrinx, and lack of abnormal contrast enhancement.¹⁶ In the series of Klekamp et al, the syrinx occurred above the level of arachnoiditis in approximately 40% of patients, below the level of arachnoiditis in 20 to 25%, and both above and below in 30 to 40%.¹⁷ Older studies had reported the relative success of syringoperitoneal shunting in treating patients with syringomyelia secondary to adhesive arachnoiditis.¹⁸ Since then, it has become obvious that most syrinx shunts are likely to fail, and once they fail, revisions are fraught with complications.^{17,19} Subsequently, the more recent literature has reported improvement in outcomes when shunting procedures

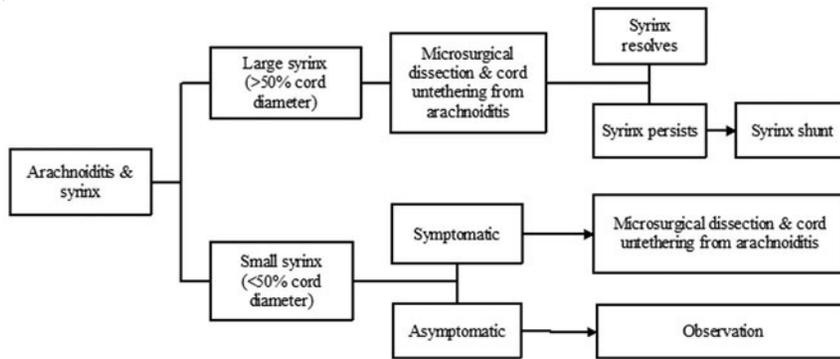


Fig. 31.9 Arachnoiditis algorithm

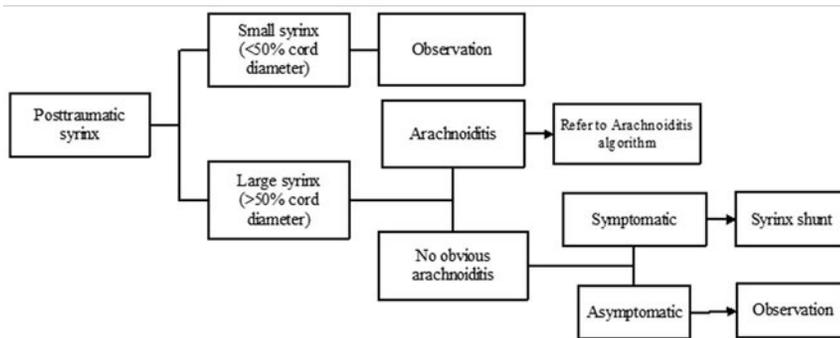


Fig. 31.10 Trauma algorithm

were abandoned in favor of microsurgical dissection and untethering of the cord.^{19,20} In such cases, it is hypothesized that decompressing the part of the spinal cord that is tethered by the arachnoiditis leads to the re-establishment of subarachnoid patency and physiologic CSF flow.^{17,21,22} Regardless of the treatment modality, however, these patients continue to experience unpredictable rates of syrinx recurrence (see Arachnoiditis algorithm, ► Fig. 31.9).^{17, 22}

31.3.8 Trauma

Although uncommon, syringomyelia is a well-known sequela of spinal cord trauma.^{23,24} Syringomyelia secondary to trauma is of clinical importance because of both the potential for progressive neurologic deterioration and the opportunity for successful surgical management when it is diagnosed. The exact incidence of symptomatic syringomyelia after trauma is unknown but is estimated to be 2 to 5%; however, the incidence of symptomatic syringomyelia in patients with spinal cord injury has been reported to exceed 50% in some series.^{25,26} Additionally, the clinical picture of this condition is often complicated by the extreme temporal variability in the initial presentation of the syringomyelia, ranging between 2 months and 36 years after the initial injury.^{27,28} Posttraumatic syringomyelia can be caused by arachnoiditis, as described in the previous section; alternatively, spinal cord contusion or infarction with hematoma may evolve into necrosis and cavitation.³² Although most small posttraumatic syrinxes remain stable, focal arachnoiditis can cause further injury to the spinal cord, perpetuating syrinx evolution. Regardless of the mechanism, once the initial cyst forms, subsequent events must take place that result in further enlargement and development of the syrinx. Perhaps surprising is the

documentation that most patients seeking medical attention for posttraumatic syringomyelia report relatively minor trauma. Despite these epidemiologic data, studies of posttraumatic syringomyelia most often involve patients with either complete or incomplete spinal cord injury who have been rendered paraplegic or quadriplegic as a result. Bonfield et al³³ identified 22 studies that met inclusion criteria and determined that all of the studies had evidence of poor or very poor quality, with no randomized controlled trials or multicenter series. Despite the poor quality of the evidence, these investigators were able to conclude that patients with complete spinal cord injury have a higher risk for syringomyelia than those with incomplete injury. Pain is by far the most commonly reported presenting symptom in this group of patients with syringomyelia.^{17,34,35} Additionally, patients have reported sensory loss, paresthesias, progressive weakness, and less commonly ataxia, spasticity, sphincter disturbance, swallowing dysfunction, and autonomic dysfunction. It should also be noted that in numerous studies, the severity of symptoms did not correlate with the size of the syrinx cavity.^{36,37}

Treatment of an Enlarging Syrinx or Progressive Symptoms

When there is progression of neurologic deficits, surgical treatment of the syrinx may become important (see Trauma algorithm, ► Fig. 31.10). However, spinal cord trauma often causes progressive cord atrophy leading to neurologic deterioration that does not respond to any surgical intervention.⁴⁰ Therefore, before the patient is committed to a surgical procedure, careful review of the MR images should differentiate between a syrinx that expands the spinal cord versus an ex vacuo cyst with

associated cord atrophy.^{38,39,40} Furthermore, although it is well established that a progressively enlarging syrinx should be treated surgically, controversy remains regarding the most effective type of treatment. Few authors recommend draining the syrinx with a stent or shunt, with the distal end of the shunt placed in the subarachnoid space, pleura, or peritoneum. Although early reports of these techniques showed encouraging results, long-term outcomes have been disappointing at best, with an 80 to 100% syrinx recurrence rate in one series.¹⁷ Based on a systematic review of the literature, the preferred surgical technique for posttraumatic syringomyelia is spinal cord untethering with expansile duraplasty, although it must be reiterated that this recommendation is based on case series only.³³

Treatment of a Stable Syrinx with Associated Pain

Posttraumatic syringomyelia is occasionally related to ex vacuo cavitation from a hemorrhagic contusion rather than from cystic expansion secondary to obstruction, and the pain

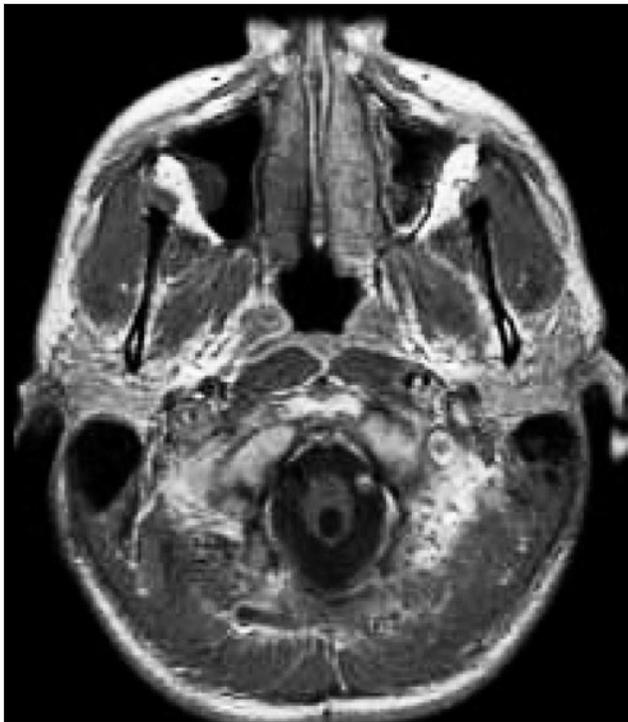


Fig. 31.11 Syringobulbia secondary to a cervicomedullary hemangioblastoma. The cyst decreased significantly in size within a year of tumor resection.

associated with such syringomyelia does not ordinarily respond to surgical treatment of the syrinx. In these cases, other methods of treatment for the pain have been attempted, including spinal cord stimulation, intrathecal morphine pump, thalamotomy, dorsal root entry zone (DREZ) procedures, and others, all of which have shown variable but usually poor results. Outcome reporting in the population with trauma is difficult because the end points of success and failure are not well demarcated. In addition, survival in this group is often decreased, preventing adequate long-term follow-up and assessment.

31.3.9 Tumors

Tumors pose an interesting diagnostic dilemma in patients who have a cyst within the spinal cord parenchyma. Of course, syringomyelia can be associated with posterior fossa tumors,^{41,42} as well as spinal tumors that are extradural; in such cases, the syrinx almost always responds to treatment that is directed primarily at the tumor. However, our interest in this chapter is to present the association between syringomyelia and tumors arising in the spinal cord proper. These cystic structures can be seen in 25 to 60% of all patients with intrinsic spinal cord tumors (refer to the chapters on spinal cord tumors.^{43,44,45,46} The tumor types most likely to cause syringomyelia are ependymomas and hemangioblastomas (► Fig. 31.11) and, less frequently, astrocytomas of any grade. Syringes associated with spinal tumors can be classified into two main types: cysts caused by an obstructive phenomenon that interrupts CSF flow, akin to syringes with other etiologies; and tumor cysts caused by the secretion of fluid by tumor cells, similar to the cysts that accompany intracranial gliomas. Whereas obstructive syringes contain fluid identical to CSF, true tumor cysts contain fluid with a high protein concentration. Certainly, as in the brain, true syringes and proteinaceous cystic cavities should be distinguished from tumor necrosis. A necrotic cavity, by definition, carries a worse outcome because it may denote a higher-grade tumor; in addition, such a cavity is ordinarily lined with tumor cells, which may influence the type and extent of resection needed. The main treatment option in patients with tumor-associated cysts is tumor resection, with little need for direct syrinx drainage (see relevant chapters in this textbook and Tumor algorithm, ► Fig. 31.12). In their review of 44 patients who had von Hippel-Lindau disease with spinal hemangioblastomas, Lonser et al⁴⁵ showed that the syrinx resolved in all patients after tumor removal, regardless of whether or not the syrinx cavity was entered.

31.3.10 Other Spinal Abnormalities

A number of other anatomical findings have been associated with syringomyelia, including spinal stenosis, herniated nucleus

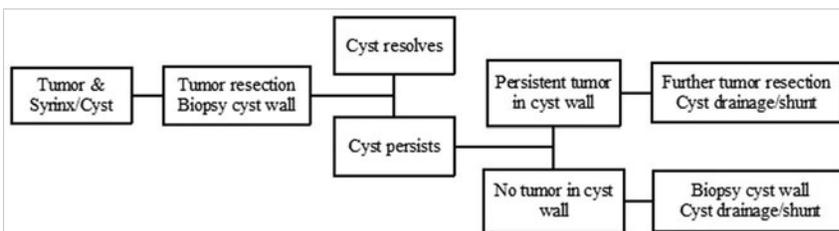


Fig. 31.12 Tumor algorithm



Fig. 31.13 Small syrinx associated with a disk herniation in a patient with radiculopathy and sensory loss over the shoulder and upper arm. This case exemplifies the difficulty in determining a cause-and-effect relationship between the cyst and the spondylosis, especially when the symptoms are poorly localizing.

pulposus (► Fig. 31.13), spinal subluxation, vascular malformations, and severe kyphoscoliosis. Patients with congenital problems such as achondroplasia (► Fig. 31.14), osteogenesis imperfecta, mucopolysaccharidosis, and others are likely to have spinal deformities such as craniocervical compression and spinal stenosis, some of which are associated with syringomyelia. Although treating the inciting etiology (e.g., disk herniation) is often sufficient to bring on resolution of the cystic cavity, it is important to ensure that the two lesions are related, not coincidental (see Other spinal anomalies algorithm, ► Fig. 31.15).⁴⁷ For instance, it is not unusual to encounter a small syrinx in association with an incidental disk bulge. The readers are cautioned about prematurely assuming a cause-and-effect relationship between the two pathologies.

31.3.11 Idiopathic Syringomyelia

Idiopathic syringomyelia is a diagnosis of exclusion made when no other treatable pathology can be identified. This category most likely represents a collection of abnormalities with varied etiologies that are difficult to discern. The best example is that of the Chiari 0 malformation, in which idiopathic syringomyelia is presumably relieved by posterior fossa decompression. This may indicate that the foramen magnum is abnormal, although such abnormalities are not evident on imaging studies. It is reasonable to think that with the availability of more accurate diagnostic measures (better flow studies, MR imaging sequences that can demonstrate subtle arachnoiditis, or even MR imaging spectroscopic techniques that may show evidence of trauma to the cord not visible on standard imaging), some of the diagnostic problems seen with idiopathic syringomyelia will be resolved. Most idiopathic syrinx cavities are small and discovered on MR imaging performed to investigate possible causes of scoliosis or pain (► Fig. 31.16).^{48,49,50} They may represent a large central canal and consequently seldom progress. However, some syrinxes are large and progressive, necessitating surgical treatment. The treatment of idiopathic syringomyelia should be guided by the cyst's anatomical characteristics and the patient's clinical status. Important characteristics include size (length

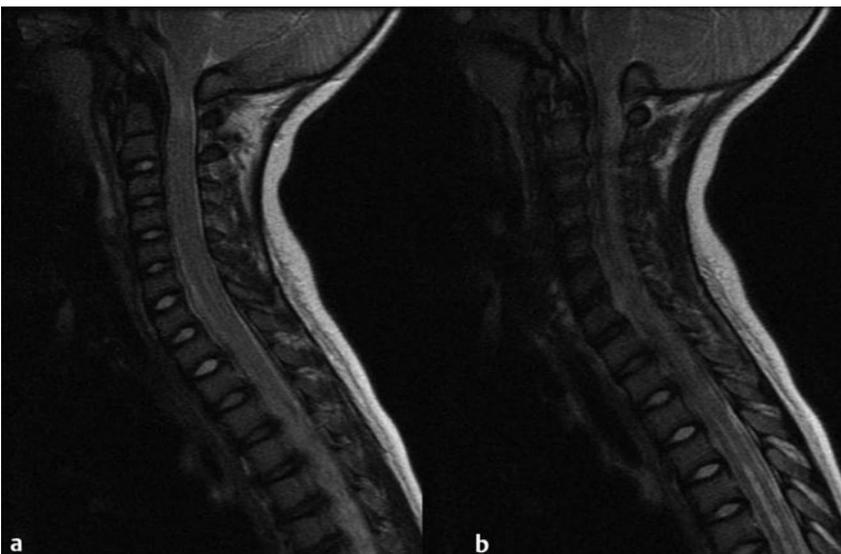


Fig. 31.14 (a) Infant with achondroplasia who presented with craniocervical stenosis and upper cervical signal abnormality on T2-weighted images, indicating cord compromise at that level. (b) Note the associated syringomyelia in the low cervical and upper thoracic region.

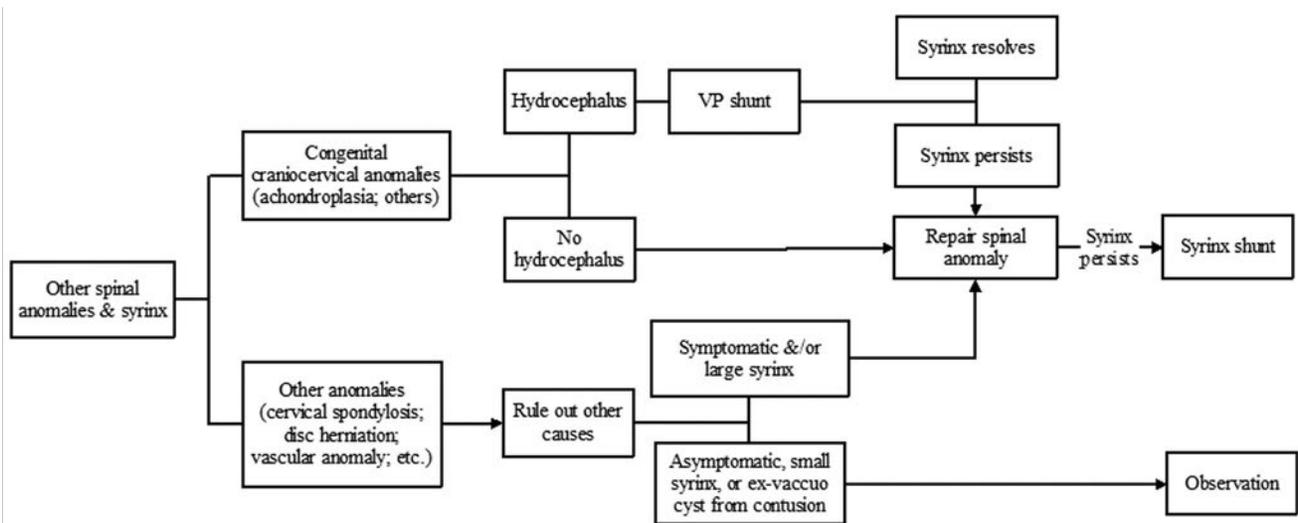


Fig. 31.15 Other spinal anomalies algorithm



Fig. 31.16 Idiopathic “thin” syrinx, likely representing an enlarged central canal and not requiring treatment.

and width), whether the spinal cord is enlarged or thinned out by the cyst (ratio of cyst diameter to cord diameter), and whether it is atrophic. It is crucial to ascertain whether the cyst is an ex vacuo result of a spinal cord injury, inflammation, infection, or vascular event, as opposed to the result of a disturbance in CSF flow leading to a buildup of pressure within the spinal canal, which would be caused by arachnoiditis, veils, or infection. The symptomatic state of the patient may also determine treatment. Ex vacuo cysts may be associated with symptoms such as central pain and dysesthesias and may even be associated with a stable motor or sensory deficit caused by the inciting event (infection, stroke, unrecognized trauma). Ordinarily, such cysts are not drained. Instead, treatment is directed at the symptoms (i.e., pain) with the use of various drugs or even surgical augmentative procedures (e.g., spinal cord stimulation) or ablative interventions (e.g., thoracic DREZ,⁵¹ thalamotomy).

Thin idiopathic syrinxes are usually asymptomatic. They are often indistinguishable from a large central canal (a normal variant^{48,52} that may occupy a significant length of the spinal cord) or a ventriculus terminalis⁵³ (a small cystic structure located at the tip of the conus medullaris, often extending into the filum terminale and representing an embryologic remnant of the terminal ventricle). In a multi-institution review of 48 patients with idiopathic syrinxes, 32 of whom had clinical and radiographic follow-up with a mean of 24 months, 28 of 32 had stable or improved symptoms, and 28 of 32 had stable or decreased syrinx size.⁵⁰ Based on this report, it may be concluded that most idiopathic syrinxes are unlikely to worsen. However, a syrinx can be labeled idiopathic only after a thorough investigation to detect possible underlying causes, including the following: subtle spinal cord tumors, arachnoiditis, arteriovenous fistulas, disturbance of the foramen magnum CSF flow, subtle anatomical abnormalities at the foramen magnum that could lead to the diagnosis of Chiari 0,^{7,8} and a tethered spinal cord from a tight filum terminale with a normally positioned conus medullaris.⁵⁴ ⁵⁵ If no cause can be identified and the syrinx is enlarging or the symptoms are worsening, there are several options for

treatment (see Idiopathic and Chiari 0 algorithm, ► Fig. 31.6): (1) direct shunting of the syrinx (syringo-subarachnoid, syringopleural, or syringo-peritoneal shunt); (2) posterior fossa decompression; (3) tethered cord release; and (4) observation and serial imaging. Such decisions can be very difficult and are usually made on a case-by-case basis depending on the clinical presentation.

31.4 Clinical Syndromes

The clinical presentation of patients with syringomyelia is diverse and depends on two main factors: the anatomy of the cyst cavity (location and size) and the etiology of the syrinx. For this reason, we have described the different clinical presentations under various etiologic subheadings. The readers are referred to the literature for discussions of the more typical neurologic syndromes seen with syringomyelia, including dissociated sensory loss, central cord syndrome, and brainstem signs, and the less typical Lhermitte phenomenon,¹ hand deformities,⁵⁶ neurogenic arthropathies (Charcot joints),^{57,58} and hyperhidrosis.^{1,59} However, a short discussion of scoliosis and pain is relevant.

31.4.1 Scoliosis

Scoliosis that occurs in association with syringomyelia is assumed to have resulted from lateralized anterior horn compression, creating an inequality of paravertebral muscle strength, with subsequent collapse of the vertebral canal.⁶⁰ In patients who present for a work-up of scoliosis, young age at presentation, atypical curve, rapid curve progression, and back pain have been found to correlate with associated syringomyelia.⁶¹

Treatment of the Syrinx

When associated with other clinical manifestations, there is little doubt that the syrinx or its etiology should be treated because treatment has shown better results in comparison to bracing or observation.^{60,62,63} However, there is some controversy as to whether syrinx treatment is indicated in the setting of scoliosis without other symptomatology and without radiographic progression of the cyst cavity. The advantage of early treatment is that if the scoliosis curvature is mild to moderate,^{60,62,63,64} the likelihood that the syrinx will stabilize without the need for fusion is high. This has also been demonstrated in scoliosis of other causes. For instance, Pierz et al showed that tethered cord release in patients with spina bifida improves curves that measure less than 20 degrees, whereas fusion is eventually required for most curves that exceed 30 degrees.⁶⁵ Furthermore, surgical management of scoliosis with an unrecognized syrinx is reported to increase neurological complications.⁶²

Treatment of the Scoliosis

Depending on the patient's age and rate of progression of the spinal curvature, corrective surgery (spinal fusion) may be necessary. The goal is to prevent progression, relieve medically intractable pain, and prevent incapacitating deformities. However, scoliosis surgery is associated with considerable risk for blood loss and neurologic injury; therefore, such a decision

requires extensive planning and a multidisciplinary approach. In some situations, bracing can be considered as a temporizing measure until the child is older or until there is evidence of progression of the curvature. Finally, it is important to reaffirm that when syringomyelia is the cause of the scoliosis, the syrinx should be treated first.⁶²

31.4.2 Pain

Spinal cysts, especially those associated with severe spinal cord trauma, can present with pain perceived to be of central origin (i.e., arising in the injured spinal cord).⁵¹ Specifically, two different pain syndromes develop in patients after spinal cord injury: (1) segmental or radicular “dull and aching” pain occurring just below the level of the injury, often in the transitional zone, which is thought to result from direct injury to the nerve roots or arachnoiditis;(2) diffuse, burning pain occurring below the level of injury and involving the entire body below or remote regions (“phantom limb” pain).⁶⁶ Because syringomyelia is associated with pain in the majority of these patients, it is virtually impossible to separate the symptoms related to the initial spinal cord damage from those related to the cyst. In fact, shunt placement in the cyst rarely results in diminution of the pain. Therefore, unless the cyst is large or enlarging, it is not usually treated surgically. Instead, treatment is directed at the symptoms with the use of various drugs or even surgical interventions such as spinal cord stimulation, DREZ, thalamotomy, and others.

31.5 Diagnostic Imaging

31.5.1 Static Magnetic Resonance Imaging

Most of the diagnostic issues related to syringomyelia rely exclusively on MR imaging. An uncomplicated syrinx is filled with fluid that is isointense to CSF on T1- and T2-weighted sequences.⁶⁷ High concentrations of fluid in the cord adjacent to the syrinx may represent gliosis.⁴³ The walls of the syrinx cavity are often irregular, especially as the syrinx enlarges. Periodic folds, septa, or haustra are visible. The inner aspect of the cavity may appear to be septated owing to collagen bands or hyalinized blood vessels traversing the syrinx. These septa are often incomplete, allowing the syrinx fluid to communicate throughout the cavity. Syrinx cavities are not expected to enhance. Thus, if tumor is suspected, gadolinium-enhanced T1 MR images should be obtained. If the cyst enhances, it is not likely to be a true syrinx, and further evaluation for a tumor should be performed. The search for the etiology of a syrinx through imaging requires the use of enhanced MR imaging to rule out tumor and arachnoiditis, as well as full posterior fossa and spinal MR imaging to rule out Chiari malformations and tethered cord.

31.5.2 Cine Magnetic Resonance Imaging

Phase-contrast MR imaging has been used to analyze the flow of CSF through the foramen magnum in patients with Chiari 1 malformation. Some investigators have used this MR technique to report increased pulsatility of the cerebellar tonsils and

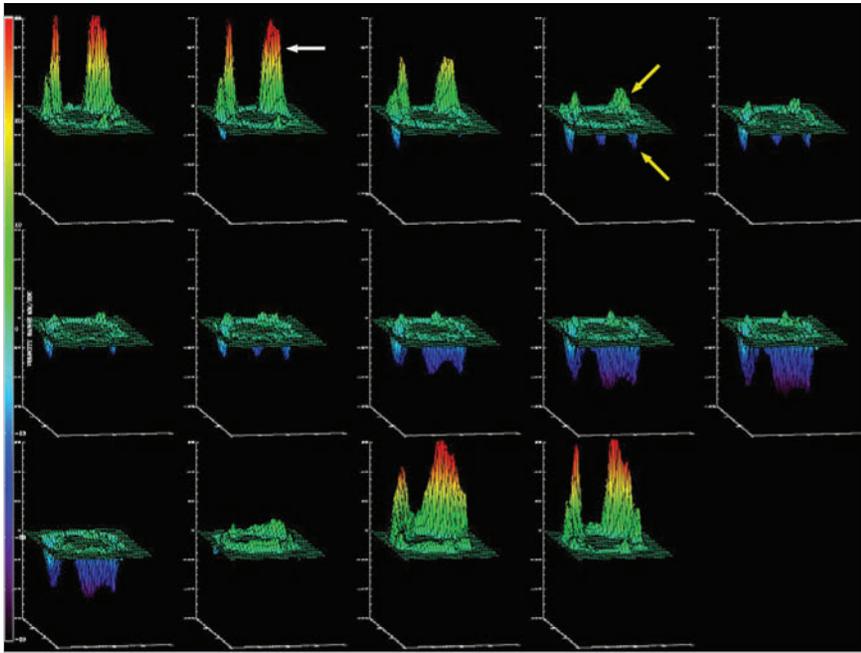


Fig. 31.17 Detailed analysis of cerebrospinal fluid flow velocities at the foramen magnum of a child with a Chiari 1 malformation. The flow velocity in each voxel is computed; all velocities are then color-coded and plotted in consecutive images representing 14 time points of the cardiac cycle. Note that there is a predominance of cephalad flow in seven of the images, and caudad flow in the other seven images. This color plot of velocities displays the cephalad velocities in green, yellow, and red, with green slowest and red fastest; caudad flow is displayed with light blue, deep blue, and violet/black, with light blue slowest and violet/black fastest. Children with symptomatic Chiari 1 show jets (*white arrow*) of elevated velocities in the anterior quadrants of the foramen magnum (red color for velocities nearing 10 cm/s). The extreme caudad velocities are not well appreciated in the surface plots because of the dark background. Finally, note the bidirectional flow (*yellow arrows*), indicating that cephalad and caudad velocities coexist at one time point. Such regional jets and bidirectionality of flow are not present in normal individuals.

spinal cord in patients with Chiari 1 malformation, suggesting that these motions may contribute to the velocity of CSF flow. In addition, phase-contrast techniques have been used to measure CSF velocities, but with no significant improvement in our understanding of the pathophysiology of these lesions.^{68,69} Phase-contrast MR imaging has been used successfully to calculate both bulk flow and average CSF velocities at the foramen magnum. Although these studies have provided data regarding the relative general obstruction of flow within the foramen magnum, and have certainly been helpful in evaluating patients with severe flow obstruction, they have failed to show a consistent difference between normal subjects and those with Chiari 1 that is mild or not yet symptomatic. In 1994, Armonda et al suggested that there is spatial heterogeneity in CSF velocity at the foramen magnum, which seems to correlate with symptoms.⁷⁰ However, to date these techniques have been largely unable to determine which patients are likely to benefit from surgical intervention.⁷¹ According to the Monro-Kellie doctrine, CSF flow through the foramen magnum is dictated by the intracranial systolic pressure wave. The volume of CSF moving in and out of the cranial vault through the craniocervical junction is therefore not affected by the size of the foramen magnum. Instead, any process that restricts flow within a portion of the foramen magnum is more likely to increase the velocity of flow than to decrease the volume of flow. When fluid moves at a constant rate through a progressively diminishing lumen, the pressure differential across the narrowed lumen progressively increases, causing fluid to move with greater velocity. Similarly, when fluid moves intermittently through a narrowed foramen magnum, the pressure differential across the foramen magnum is increased. Hypothetically, tonsillar herniation, adhesions within the foramen magnum, and other processes that narrow the foramen magnum increase the average bulk flow and velocity through that region. Under anatomically homogeneous circumstances, such a theory can be successfully applied to the Chiari 1 malformation. However, because of the anatomical

variability related to the tonsillar herniation, such pathophysiologic explanation does not suffice. In their preliminary studies, Haughton et al built upon the information collected from previous studies of CSF velocity and bulk flow in an effort to study the extent to which such flow is spatially or temporally heterogeneous. Specifically, they found significant elevation of CSF systolic or diastolic peak velocities in specific regions within the foramen magnum, but not in others⁷² (► Fig. 31.17). Moreover, they showed that these abnormally high peak systolic CSF velocities in patients with Chiari 1 exceed those in normal subjects and improve postoperatively.^{72,73} Follow-up studies revealed nonzero net flow and bidirectional flow within specific voxels in the foramen magnum, indicating that the overall flow is truly disturbed in both adults and children.^{74,75} By expanding on the various temporal and spatial indices of heterogeneity identified, it eventually may be possible to develop a comprehensive and organized understanding of foramen magnum fluid physiology, with emphasis on particular flow signatures corresponding to specific clinical scenarios. This is obviously contingent on further improvement in MR imaging and bioinformatics. The eventual goal is to understand the pathophysiology of syringomyelia and the Chiari 1 malformation in children and adults, and potentially to anticipate the onset of neurologic symptoms and signs to allow early intervention.

31.5.3 Computational Models of Syringomyelia

In recent years, researchers in biomechanical engineering and physics have taken up the challenge of studying syringomyelia and posterior fossa pathology. These groups have applied the principles of computational fluid dynamics to Chiari and syringomyelia pathologies, using hydrodynamic modeling to characterize the region of interest (i.e., the foramen magnum) and predict the interactions of its components. Computation fluid

dynamics derives its models from anatomical and flow data obtained with static and cine MR imaging. The goal is to provide both spatial and temporal models of CSF flow that can be individualized to a patient's specific parameters, and thus improve treatment and surgical planning for these conditions. For example, an early study was conducted to determine the properties of a healthy spinal canal.⁷⁶ A more recent study has shown CSF movement in the perivascular spaces of the spinal cord that is due to differences in the timing of CSF and arterial pulsations,⁷⁷ potentially lending credence to theories of syrinx pathogenesis that involve perivascular fluid movement.

31.6 Surgical Approaches

The impact of surgical treatment on the natural history of patients with Chiari malformations and syringomyelia has not been explored with randomized prospective studies. Such an undertaking would be difficult because of the perceived benefits of surgery, which include an observable improvement in symptoms and radiographic findings. Considerations that are generally agreed upon include rectifying hydrocephalus before any other corrective surgery is undertaken, and approaching the pathologic cause of the syrinx rather than the syrinx itself whenever possible. Most of the indications and algorithms are presented in the section on classification based on etiology. Surgical techniques for the Chiari malformations, tethered cord, and other etiologies are described in detail elsewhere in this textbook. Here, we briefly describe the surgical techniques used to directly drain or shunt a syrinx.

The use of syrinx-to-subarachnoid shunts is controversial. Some surgeons have used them to replace decompressive procedures,^{78,79,80} whereas others have used them concomitantly with surgery for the causative problem, such as suboccipital decompression for a Chiari 1 malformation. Current recommendations, however, suggest treating the pathology associated with the syrinx first, if at all possible. When the syrinx is not amenable to treatment in that fashion, syrinx shunting should be considered. Syrinx shunting may also be considered in patients with severe arachnoiditis who are likely to fail lysis of adhesions (see Recurrent syrinx algorithm, ► Fig. 31.18). This is advocated as a primary therapy in cases of posttrau-

matic syringomyelia with no obvious associated arachnoiditis and with a low level of suspicion for a foramen magnum CSF flow problem. Shunting is not limited to the subarachnoid space; shunts can be placed in the pleural space and peritoneal space as well. This procedure may be effective if shunting to the subarachnoid space is complicated by severe arachnoiditis or other anatomical problems within the spinal canal.

31.7 Conclusion

The diagnosis and treatment of syringomyelia can significantly impact the progression of symptoms and may improve neurologic outcomes regardless of the duration of the pathology. However, patients who have not had long-standing symptoms fare better than those with debilitating deficits. The advent of MR imaging has improved the timely diagnosis of syringomyelia before significant neurologic progression. Treatment varies with the type of pathology present. Because no single theory has been able to explain the pathogenesis of syringomyelia, a clear approach to treatment continues to evade physicians. A combination of clinical judgment, anecdotal reports, and case series data is used to provide patients with conservative or surgical options. Restoration of normal CSF flow is the goal of most operative interventions. Thus, in many cases, it is advised that the underlying pathology be treated rather than the syrinx directly. We suggest that syrinx shunting should be reserved for patients who do not respond to first-line surgery. In fact, some surgeons consider that a failed first-line therapy should be repeated or improved upon before a syrinx is drained directly. Moreover, idiopathic syringomyelia may well represent a collection of disorders with origins that are yet unidentifiable with current diagnostic techniques. Chiari 0, or posterior fossa abnormalities without obvious MR imaging correlates, which responds to craniocervical decompression, probably explains a subset of those cases. It is likely that other currently unknown origins exist as well. Finally, it is important to recognize the impact of hydrocephalus. Hydrocephalus should be diagnosed and treated before any other surgical procedure is undertaken. With astute clinical acumen, knowledge of anatomy, and an understanding of the conditions associated with syringomyelia, physicians will continue to alleviate symptoms and advance the study of this disease.

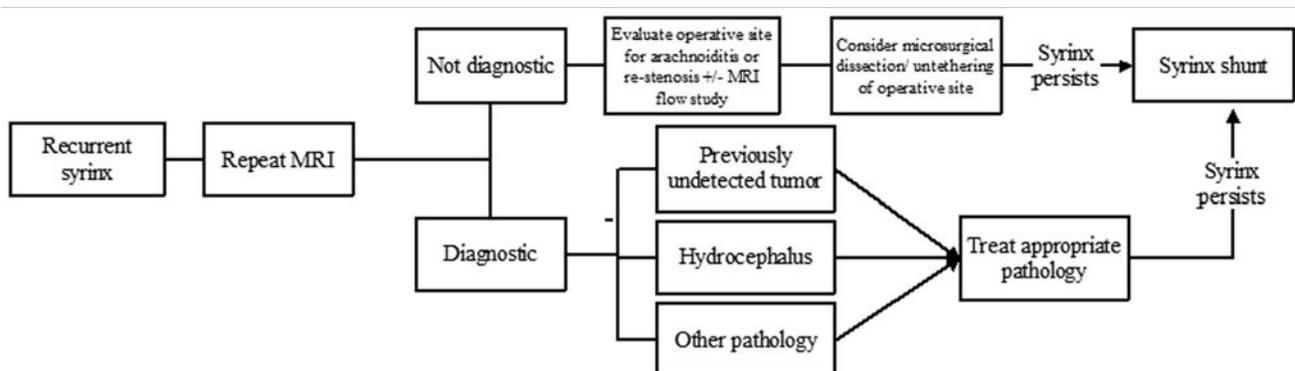


Fig. 31.18 Recurrent syrinx

Pearls

- Syringomyelia is a cystic cavitation of the spinal cord caused by different cranial and spinal abnormalities, such as Chiari malformation, tumor, and trauma.
- The pathophysiology of syringomyelia remains misunderstood, but the use of evolving MR imaging technology may help elaborate such a mechanism of pathogenesis.
- The fundamental goal in the diagnosis of syringomyelia is to identify the etiology of the cyst.
- The management of symptomatic syringomyelia is best approached by treating the associated condition thought to have caused the syrinx, thus re-establishing CSF flow and subarachnoid patency. Direct syrinx shunting should be used only as a last resource.
- A small and asymptomatic syrinx will often not require treatment.
- Chiari 1-related syringomyelia is best treated with posterior fossa decompression.
- Chiari 2-related syringomyelia should be assumed related to CSF shunt malfunction until it is proven otherwise, regardless of brain imaging findings.
- Syringomyelia may recur many years after the initial treatment. Thus, patients with a syrinx should be followed on a long-term basis, both clinically and radiographically.

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32 Scalp and Skull Neoplasms

Dale M. Swift and David J. Sacco

Children are frequently evaluated by neurosurgeons and other medical professionals for bumps on the head, but in reality neoplasms of the scalp and skull are relatively rare. In the pediatric population, tumors in this location comprise a diverse array of pathologies quite different from those seen in adults. Pediatricians, dermatologists, plastic surgeons, general surgeons, and otolaryngologists, as well as neurosurgeons, commonly evaluate children with scalp or skull masses. Therefore, clinical experience with these relatively rare lesions is limited in any given practice. The published medical literature reflects this, consisting mostly of case reports, which tend to concentrate on atypical presentations and small case series that are limited by patient preselection.¹ Standardized protocols for the evaluation and treatment of children with scalp and skull tumors are lacking.²

Pediatric neurosurgeons are uniquely equipped to treat masses of the scalp and skull. Experience gained with modern techniques of craniofacial surgery charges the surgeon to consider the aesthetics of reconstruction as well as the efficacy of resection in the treatment of these lesions. Knowledge of the natural histories of specific neoplasms of this region, as well as familiarity with current adjuvant treatment regimens, will assist the neurosurgeon in planning both the resective and the reconstructive procedures.

32.1 Differential Diagnosis

The majority of “lumps on the head” called to medical attention are not neoplastic. Congenital, posttraumatic, and inflammatory lesions frequently present as masses of the calvaria. An extremely wide range of pathologies appears in this location. General reviews of surgically treated scalp and skull masses in children show that about one-half are dermoid cysts.^{3–6} The remaining diagnoses consist of a wide variety of dissimilar lesions (► Table 32.1).

The diagnosis is often obvious on physical examination; at other times, radiographic or histologic examination is necessary. Patients referred for evaluation of a scalp “lesion” or “mass” sometimes have an atypical form of an otherwise easily recognizable diagnosis, such as a meningoencephalocele. Congenital lesions are discussed in other chapters of this book and are included here for completeness only. Entities such as Langerhans cell histiocytosis, aneurysmal bone cyst, and fibrous dysplasia may not be truly neoplastic, but they share presentation and treatment patterns with neoplasms and thus are included in this chapter.

32.2 Clinical Presentation

The presenting signs and symptoms of various scalp and skull lesions in children are quite similar, regardless of the primary pathology. The most common complaint is a visible or palpable mass. Congenital lesions may be noticed at birth by the examining physician or the parents. Birth-related swelling of the scalp may obscure a congenital lesion or cephalohematoma that will

later become obvious. Newborns and infants with high-flow vascular malformations may have signs of high-output heart failure, including failure to thrive and cardiac murmurs.

Some lesions are painful or tender to palpation. In preverbal children, pain may be expressed as irritability or failure to thrive. Careful neurologic examination is important, but newborns and infants may harbor surprisingly large intracranial masses and still exhibit a neurologic examination findings appropriate for their chronological age. Head circumference remains one of the most valuable measurements in the assessment of young children. Abnormal tufts of hair, discoloration of the scalp, and palpable skull defects may all present for neurosurgical evaluation at various ages. In older children, it is important to determine whether the lesion has changed in size or character recently. Not uncommonly, patients are referred by a general pediatric surgeon or dermatologist after lesions previously thought to be confined to the scalp have been found to extend through the calvaria.⁷

32.3 Diagnostic Studies

Most children referred to a neurosurgeon for the evaluation of a scalp or skull mass undergo imaging with computed tomography (CT) or magnetic resonance (MR) imaging. Ultrasound, however, is frequently used as a screening examination in

Table 32.1 Masses of the scalp and skull

Etiology	Lesion
Congenital	Aplasia cutis congenita Dermoid cyst/dermal sinus tracts Atretic meningocele/meningocephalocele Nevus sebaceus
Neoplastic <ul style="list-style-type: none"> • Benign • Malignant 	Neurofibroma Osteoma, osteoid osteoma, osteoblastoma Fibrous dysplasia Ossifying fibroma Giant cell tumor Aneurysmal bone cyst Melanotic neuroectodermal tumor of infancy Neuroblastoma Lymphoma Ewing sarcoma Osteogenic sarcoma
Posttraumatic	Calcified cephalohematoma Growing skull fracture (leptomeningeal cyst)
Vascular	Hemangioma Sinus pericranii Arteriovenous fistula/cirroid aneurysm
Inflammatory	Langerhans cell histiocytosis Lymphadenopathy Necrobiotic nodules (benign rheumatoid nodules/ subcutaneous palisading granulomas) Myofibromatosis Cranial fasciitis Osteomyelitis

newborns.⁸ Indeed, some form of neuroimaging is recommended for all but the most obvious of extracranial masses. Up to one-third of patients evaluated for a solitary nontraumatic lump on the head have some degree of intracranial extension.³ Occasionally, a predominantly intracranial process, such as a subdural empyema or even a brain tumor, may present with scalp swelling, especially in infants.³

Midline or pedunculated scalp masses should be evaluated with MR imaging to assess the degree of intracranial extension and any relation to the dural sinuses. For smaller scalp lesions, the abnormal area should be marked and called to the attention of the radiologist before scanning. MR imaging is generally preferable to CT for evaluating soft tissue masses and the diploic space of the skull. CT is superior for bony masses. The two imaging modalities, however, are frequently complementary (► Fig. 32.1a,b and ► Fig. 32.2).⁸ Many skull and scalp lesions are not well visualized on routine axial CT. Vertex skull lesions are obscured on axial images tangential to the lesion, so direct coronal or thin-section cuts with three-dimensional reconstruction are necessary for improved visualization. CT protocols should be specific for children to limit the radiation dose.⁹ Radionuclide bone scans should be reserved for lesions whose imaging characteristics are suggestive of possible multifocal pathology (e.g., Langerhans cell histiocytosis, Ewing sarcoma).

32.4 Surgical Concepts

In children with scalp or skull tumors, surgery is indicated for the decompression of neural structures, curative or palliative resection, correction of disfiguring deformities, relief of pain, or biopsy of an unknown lesion. Given the low complication rate of craniotomy for the resection of skull lesions, total excision is generally performed rather than biopsy.² It is not the intent of this chapter to describe specific surgical techniques, but rather to provide an overall framework for approaching the surgical management of these patients. All resective procedures should be planned in anticipation of a reconstructive procedure. It is the authors' belief that the psychosocial effects of a cranial defect or a cosmetically disfiguring scar on a developing child, as well as the attitudes of others toward the child, should never be minimized.

In many cases, the defect left by the resection of a skull tumor may be repaired primarily with a split-thickness bone graft taken from adjacent cranium. Accordingly, the scalp incision should be designed to allow maximum vascularity as well as access to potential donor craniotomy sites (► Fig. 32.3d and ► Fig. 32.4c). Despite its length, the standard coronal scalp incision is frequently the best choice. In situations in which poor wound or graft healing is anticipated (e.g., when radiation or chemotherapy is indicated), the reconstruction should be delayed until healing conditions are optimized. This may help avoid the loss of both donor and recipient grafts due to poor wound healing and/or infection.

The need for intradural exploration is usually apparent from the preoperative imaging studies. Although most scalp or skull tumors do not demonstrate intradural extension, congenital lesions such as dermoid sinuses frequently have a definite connection to the underlying brain that must be appreciated. Failure to completely excise a dermal tract may allow growth of the

residual intracranial component or result in delayed infection.¹⁰ Missed intracranial extension¹¹ and postoperative adhesion of the brain to overlying dura¹² have been reported to cause focal neurologic symptoms analogous to spinal cord “tethering.” Thus, intradural exploration should be performed when transdural extension is apparent. The presence of dural enhancement does not always necessitate opening of the dura. Many full-thickness skull lesions incite an inflammatory response in the dura, and neuroimaging reveals a “tail” of dural enhancement (► Fig. 32.3c). At the time of surgery, the tumor is often peeled off the outer dural layer, leaving the inner intact.

32.5 Lesions of the Scalp

Congenital lesions of the scalp are quite common, but actual neoplasms of the scalp are rare in children. Typical melanocytic nevi are common on the scalp.¹³ They are usually acquired, and although they may change with time, they rarely become suspicious for malignancy during childhood.¹⁴ Congenital melanotic nevi, on the other hand, are less common but require closer scrutiny for potential malignant transformation.¹⁵ Giant congenital melanotic nevi, sometimes called congenital hairy nevi, may occur anywhere on the skin, including the scalp. They are particularly distressing for families because of their conspicuous appearance. When these lesions involve the scalp or overlie the dorsal spine, abnormal collections of melanocytes may be observed in the underlying brain and meninges.¹⁶ The potential for intracranial or intraspinal proliferation in these situations is unknown. Congenital melanocytic nevi may be further classified as “compound” when the lesions involve both the dermis and epidermis. These nevi may give rise to basal cell carcinoma or malignant melanoma.¹⁷

Another type of congenital nevus requires special attention because of its known potential for malignant degeneration. Nevus sebaceus is a congenital hamartoma primarily of the sebaceous glands that may undergo transformation to basal cell carcinoma or other, more benign skin tumors.^{18–20} It appears as a hairless, slightly raised, pink or tan area, usually on the scalp but at times on the face or elsewhere. Traditionally, resection of these lesions has been recommended both for cosmetic reasons and to decrease the risk for future malignancy.^{17,18,21} The risk for malignant transformation may, however, be less than previously suspected, and therefore the timing of resection can be flexible.²² In large lesions, staged resection may be required, and scalp tissue expansion may be necessary for reconstruction after resection.²¹

In practice, dermatologists and plastic surgeons usually treat superficial lesions confined to the dermis; it is not until subgaleal or cranial involvement is apparent that neurosurgical consultation is obtained. The following conditions, although not necessarily neoplastic, are frequently encountered by pediatric neurosurgeons.

32.5.1 Scalp Nodules

Subcutaneous nodules of the scalp are common in children. Most do not extend intracranially.²³ Lesions of the midline, painful lesions, or masses that on palpation are found to be fixed to the skull may require further neurosurgical evaluation.

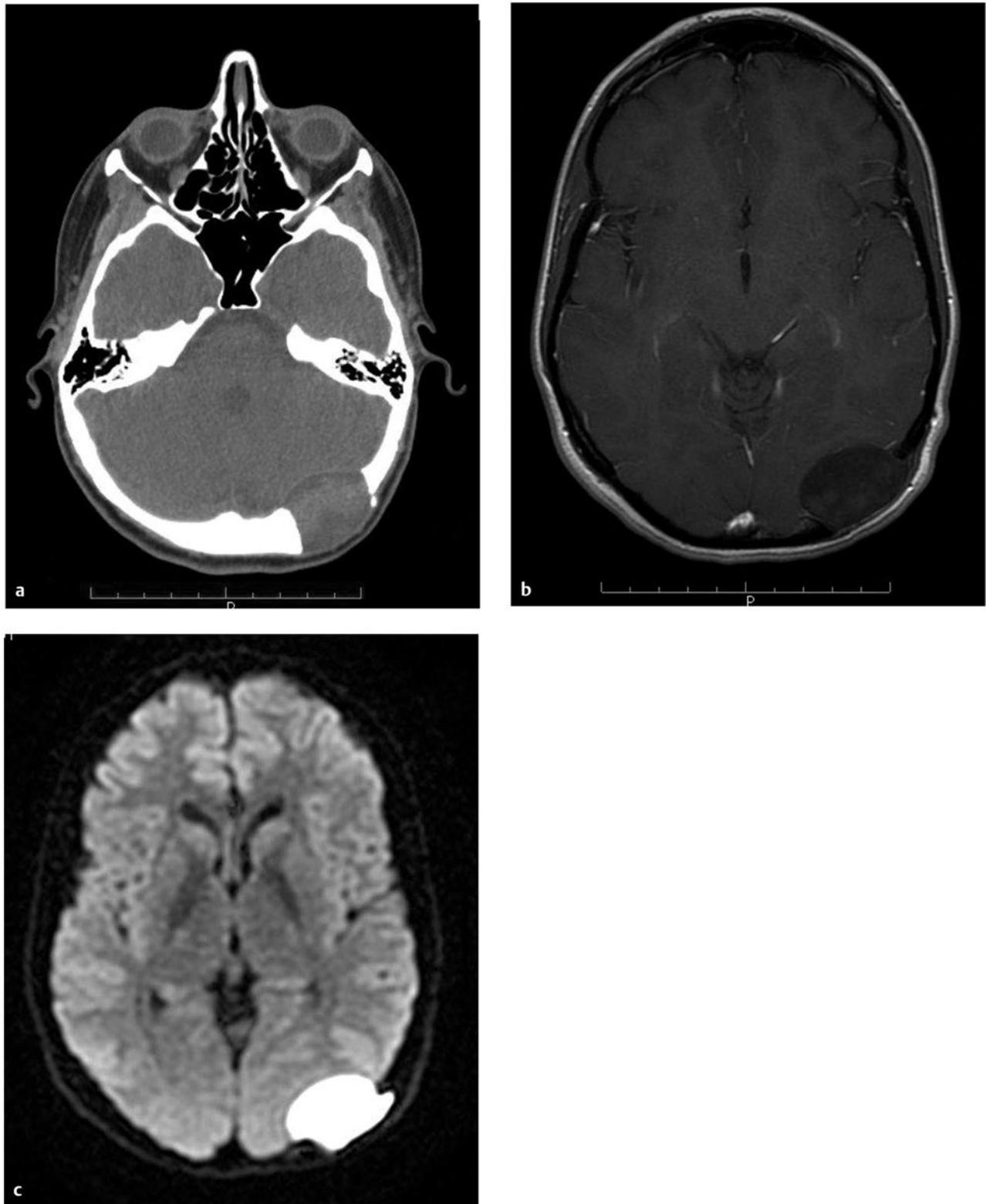


Fig. 32.1 Skull dermoid. This young adult presented with a history of a lump on the back of her head for as long as she could remember. (a) Computed tomography demonstrates a full-thickness skull defect. (b) T1-weighted magnetic resonance (MR) imaging with contrast shows a large nonenhancing occipital mass hypointense to normal brain. (c) Diffusion-weighted MR imaging reveals restricted diffusion, consistent with a dermoid cyst.

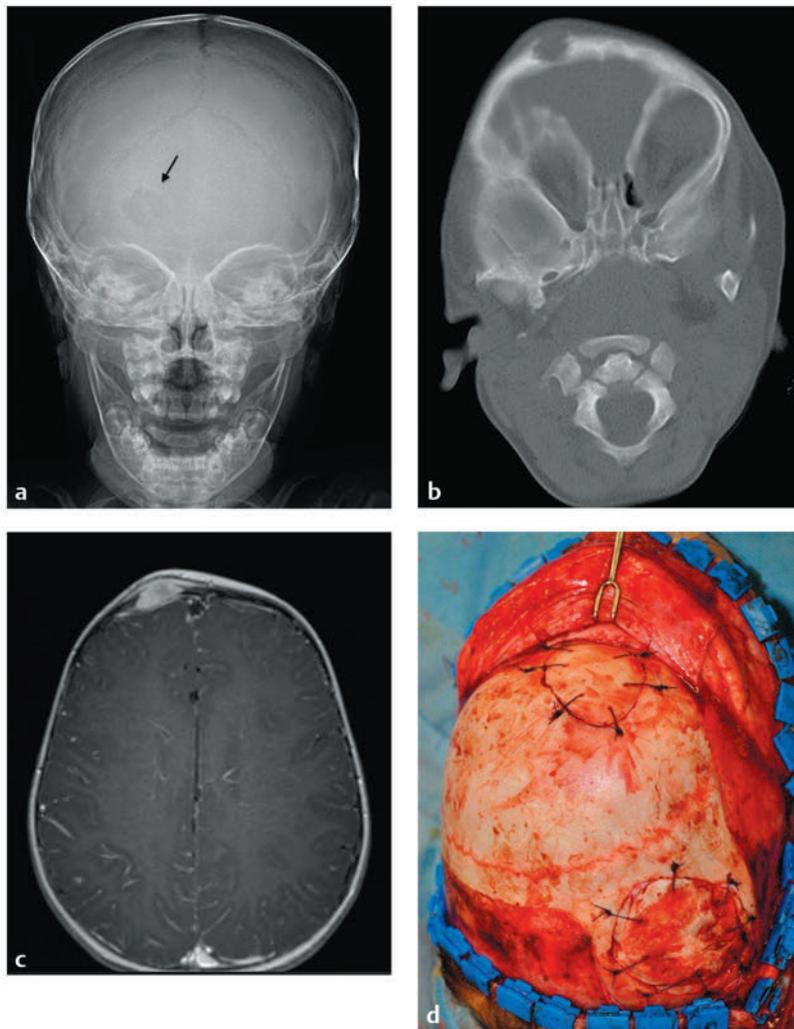


Fig. 32.2 Langerhans cell histiocytosis. This 18-month-old girl presented with swelling over the left side of the forehead. (a) Skull X-ray shows a lytic lesion with irregular but not sclerotic margins. (b) Computed tomography with bone window. (c) Axial T1-weighted magnetic resonance imaging with contrast shows marked enhancement. The lesion failed to resolve over 6 months and was completely resected. Pathology was Langerhans cell histiocytosis. (d) At the time of resection, primary reconstruction with split-thickness autologous cranial bone was performed.

Scalp nodules result from numerous processes. In children especially, enlarged lymph nodes may present as scalp nodules, particularly in the postauricular region. Lymphadenopathy appears as firm, rubbery, mobile nodules, which may be tender. There is frequently a history of upper respiratory infection, and the lymphadenopathy is self-limited. After trauma, it is not uncommon in children to notice very firm nodules fixed to the skull, with or without skull fracture. These periosteal reactions should also resolve spontaneously.

Scalp nodules associated with a tuft of abnormal hair frequently have a stalk, which may penetrate the skull to a variable extent. Although they are often assumed to represent a dermal sinus tract, these lesions may actually prove to be *heterotopic neural nodules*.²⁴ These malformations are most likely part of a continuum of developmental pathology that includes atretic meningocele, cephalocele, and encephalocele, as well as dermal sinus tracts. The location is usually midline or para-midline in the parieto-occipital regions. Despite an underlying bony defect, no intracranial pathology is usually identified apart from a persistent falcine sinus.²⁴ As a practical matter, knowledge of the histology in this clinical setting may differentiate heterotopic neural nodules from dermal sinus tracts, thus decreasing

concern regarding the need for intradural exploration and continued observation.

Neurofibromas of the scalp may accompany neurofibromatosis type 1 (NF-1) and to a lesser extent neurofibromatosis type 2 (NF-2).²⁵ With an incidence of 1 in 3,000 live births, NF-1 is a commonly observed condition in pediatric neurosurgical practice.²⁶ In a patient with NF-1 or NF-2, the discovery of painless, subcutaneous nodules of the scalp does not usually present a diagnostic problem. Occasionally, however, a nodule may be found in the absence of known neurofibromatosis. Characteristic cutaneous markings such as café au lait spots and axillary freckling should be sought, although they may not yet be present in young children. Biopsy of a lesion that shows neurofibroma, although not usually essential, will prompt consideration of the diagnosis of neurofibromatosis. Resection of neurofibromas of the scalp may be indicated when lesions are painful (e.g., in proximity to the occipital nerve) or disfiguring. Biopsy or resection should be considered in neurofibromas that have rapidly enlarged because malignant degeneration is possible. Plexiform and diffuse neurofibromas may present as disfiguring masses in the scalp and face.²⁷ Because of the diffuse nature of these lesions, complete resection is often impossible. When

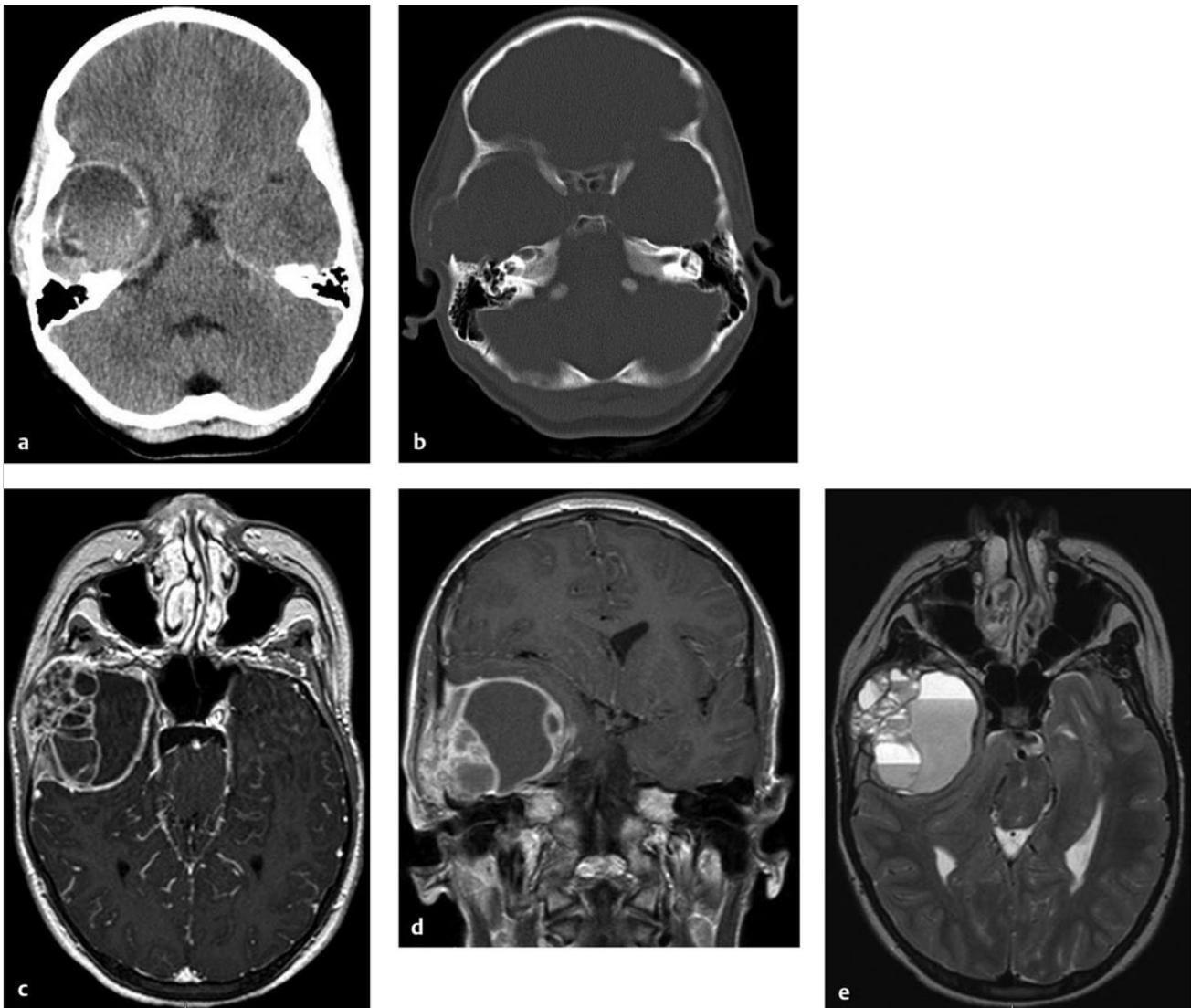


Fig. 32.3 Aneurysmal bone cyst. This 12-year-old girl presented with a nontender firm mass in the right temple. (a,b) Computed tomography shows calcification surrounding the lesion; bone windows show a thin shell of intact bone externally. (c,d) Axial and coronal T1-weighted images with contrast reveal an enhancing soft tissue portion of the tumor. (e) Axial T2-weighted image shows typical fluid–fluid levels of nonclotted blood.

indicated, subtotal debulking may be performed for large disfiguring lesions or for airway protection.

Multiple painless subcutaneous nodules of the scalp may result from an inflammatory process of unknown origin known generically as necrobiosis. Necrobiotic granulomas of the scalp are described under many titles, including *rheumatoid nodules*, *benign rheumatoid nodules*, *pseudo-rheumatoid nodules*, *subcutaneous granuloma annulare*, *xanthogranulomas*, and *subcutaneous palisading granulomas of the scalp*.^{28–30} Necrosis and degeneration of the dermal collagen are the predominant histologic features, with surrounding histiocytes and epithelioid and multinucleated cells.³⁰ In contrast to true rheumatoid nodules associated with rheumatoid arthritis, these granulomas involve the scalp and pretibial subcutaneous tissue and are not found near the joints. Progression to clinical rheumatoid arthritis does not usually occur.²⁹ The lesions have a predilection for the occipital and frontal regions of the scalp and usually resolve

spontaneously. In general, biopsy is not indicated in typically appearing lesions.^{28,29} Necrobiotic xanthogranuloma may be associated with a systemic disease such as multiple myeloma. A single case with dura-based intracranial lesions has been reported in an adult.³¹

Fibrodysplasia ossificans progressiva is a rare genetic inflammatory disorder that commonly presents with scalp nodules in infancy.³² The disease is characterized by progressive heterotopic calcification of the soft tissues, which may be stimulated by trauma or surgery. Thus, biopsy or excision may be contraindicated.³³ Patients with fibrodysplasia ossificans progressiva nearly always have a characteristic deformity of the great toes, and a definitive diagnosis can be obtained by genetic testing.³⁴ When surgery is indicated, specific anesthetic and perioperative considerations are recommended.³⁵

Despite the benign nature of the majority of scalp nodules in children, the potential for the development of malignant lesions

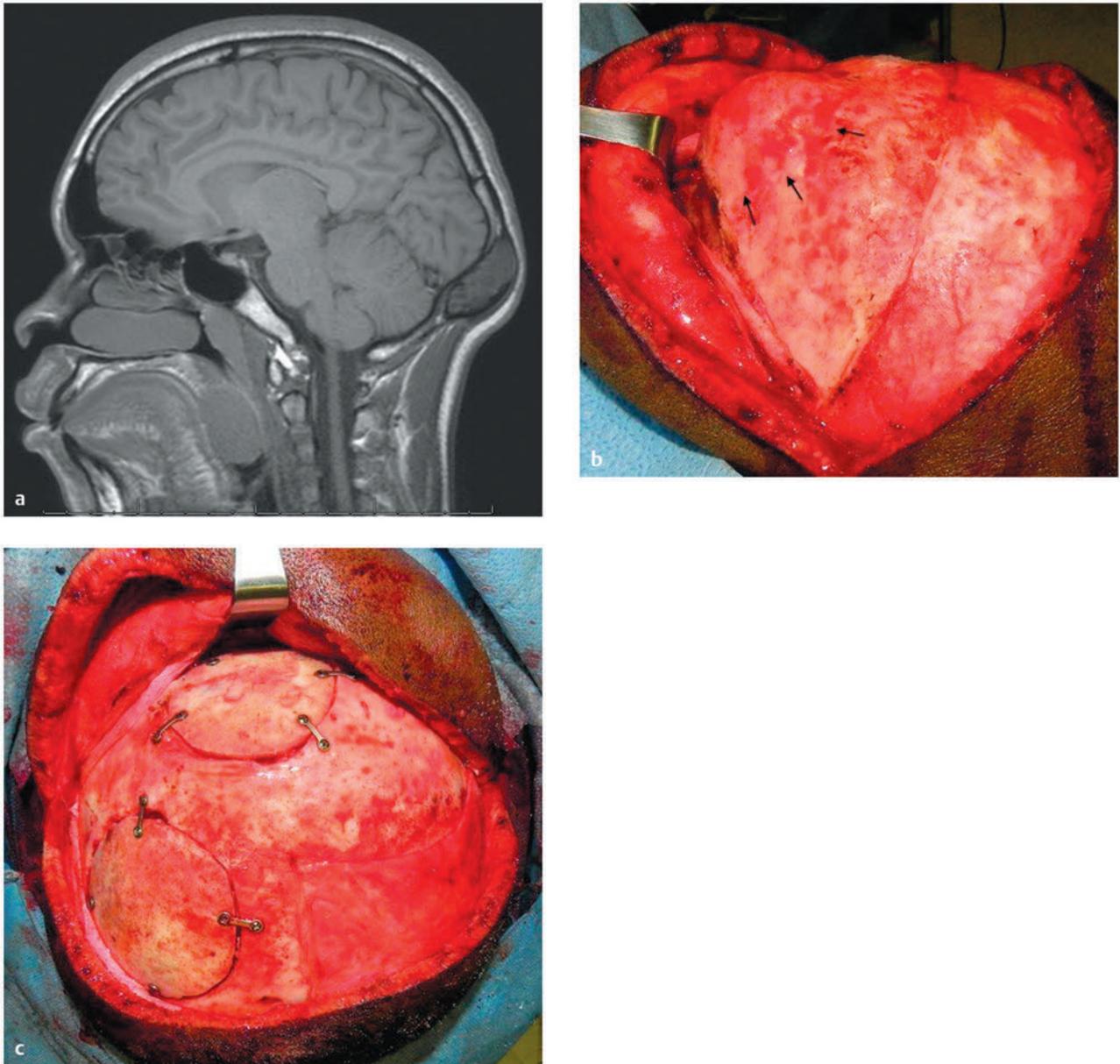


Fig. 32.4 Fibrous dysplasia. This 17-year-old young man presented with a long-standing occipital mass that had recently enlarged and became tender. (a) Sagittal T1-weighted magnetic resonance image showing isointense expansile calvarial lesion in the region of the inion. (b) Intraoperative photograph of lesion. (c) Intraoperative photograph showing reconstruction with split-thickness autologous cranial bone.

that require aggressive treatment should not be overlooked. Essentially any pathology that can affect the skin can involve the scalp. The diversity of pathologic conditions affecting the scalp is beyond the scope of this chapter, but as neurosurgeons we remain aware of the ability of the hair-bearing scalp to conceal pathologic lesions.

32.5.2 Mesenchymal Tumors

A variety of benign proliferative disorders of mesenchymal tissue occur in infancy and may result in masses involving the scalp, skull, and occasionally the dura. These lesions have

variable histologic appearances and generally have excellent long-term prognoses despite initial periods of alarmingly rapid growth. Biopsy and excision are generally performed for diagnosis and decompression. Definitive diagnosis depends on the histopathologic features, including the results of immunohistochemical studies.³⁶

Infantile myofibromatosis is a mesenchymal proliferative disorder resulting in fibrous tumors of the skin, subcutaneous tissue, muscle, bone, and viscera. Sixty percent of lesions are present at birth and 88% appear by 2 years, making this the most common fibrous tumor of infancy.³⁷ It may occur as a solitary tumor (*myofibroma*) or as multiple tumors

(*myofibromatosis*). Solitary myofibromas often occur in the head and neck and may involve the skull.^{38–43} Some lesions appear to arise from the dura and result in a significant intracranial mass effect, although the brain and arachnoid are not invaded.³⁹ Interestingly, the literature contains multiple reports of the spontaneous regression of infantile myofibromas, many of which reportedly occurred after biopsy.^{44–48} The reliability and time course of possible regression have not yet been defined, so that surgical excision is generally undertaken. If at operation dural invasion is observed, dural resection may be required.^{39,40} After complete resection, recurrence is rare, and adjuvant treatment is not indicated except in the case of multiple lesions involving the viscera.⁴⁵

The histology of infantile myofibromatosis is characterized by two populations of cells: myoid spindle cells and perivascular cells comparable to hemangiopericytoma cells.^{40,41} There are rare reports of *intracerebral* myofibromas, usually occurring in patients with multiple lesions.^{48–50} It is postulated that these rare intracerebral tumors in the setting of infantile myofibromatosis may derive from the perivascular population of cells.^{48–50} This finding is consistent with the concept of a spectrum of infantile myofibroblastic lesions consisting of infantile myofibromatosis, infantile hemangiopericytoma, and possibly congenital infantile fibrosarcoma.^{51,52}

Cranial fasciitis of childhood (CFC) is a relatively rare, benign scalp mass consisting of an abnormal proliferation of spindle cell fibroblasts in a myxoid stroma.³⁶ Initially described in 1980, CFC is now considered a subset of the more common nodular fasciitis, distinguished—as its name indicates—by a cranial location and childhood presentation.⁵³ CFC usually presents by 2 years of age as a firm, rubbery, nontender mass firmly attached to the skull, most commonly in the temporal region. The lesion is presumed to arise from the deep fascia or periosteum. These masses may grow rapidly and to alarming dimensions. Occasionally, the lesion grows predominantly intracranially, and although usually dura-based, it may rarely be purely intraparenchymal.⁵⁴ CT generally reveals an enhancing osteolytic lesion with sclerotic edges. MR imaging also shows enhancement, but with a central nonenhancing component. The enhancing region is presumed to represent the fibrous component and the nonenhancing region the myxoid matrix.⁵⁵

The etiology of CFC is unknown, but it may have a reactive component. Up to 15% of cases are associated with trauma.^{56–59} Other cases have been reported after radiation therapy⁶⁰ and at sites of prior craniotomy.⁶¹ Recently, a subset of CFC has been found to have molecular similarities to desmoid fibromatosis and Gardner fibroma.⁶²

Although spontaneous regression of CFC has been described, the reliability and time course remain unknown.^{63,64} Therefore, surgical resection of CFC is generally indicated for histologic diagnosis and relief of mass effect. Dural resection is usually unnecessary except in cases with a large intracranial extension.⁵⁴ Bone invasion should be treated with excision or curettage. Despite an appearance alarmingly suggestive of malignancy, these lesions usually do not recur, and even incompletely resected lesions may regress over time.^{58,59,65–67} Intralesional steroid injection has recently been reported to be effective in a single child with multiple small CFC lesions without skull erosion.⁶⁸ For lesions that are neither disfiguring nor of neurologic concern, this may be an acceptable option.

Desmoplastic fibroma is a benign tumor arising from bone and characterized by abundant collagen formation. It generally occurs in adults but has been reported in the skulls of infants and children.^{69,70} Radiographically, it appears as an osteolytic lesion, and although histologically benign, it can be locally aggressive. Complete surgical resection is recommended when possible because incomplete resection may result in local recurrence, and unlike the other fibrous lesions mentioned previously, it has not been observed to undergo spontaneous regression.^{69,70}

32.5.3 Scalp Defects

Failure of closure of the cranial neural tube results in a spectrum of anomalies ranging from massive encephaloceles to small skull defects through which the cranial meninges herniate without underlying cerebral abnormality. Small midline lesions, usually in the occipital region, are frequently referred to as *atretic cephaloceles* and are commonly seen in pediatric neurosurgical practice.¹ The lesions are soft and compressible, and they may increase in size with Valsalva maneuvers. The overlying skin is frequently thin, hairless, and discolored. Neural elements may be present within the cavity of the lesion with variable or no connection to the underlying brain. As noted in the preceding section, these ectopic collections of neural cells may present as scalp nodules, as well.²⁴ There are frequently associated structural anomalies of the brain seen on MR imaging.^{1,24}

Aplasia cutis congenita is a full-thickness skin defect that frequently involves the scalp. Lesions of variable size usually occur in the midline vertex.⁷¹ In 20% of cases, there is also a defect of the underlying skull.⁷² In severe cases, the dura may also be deficient, and the child may have a large area of exposed brain. Initial efforts are aimed at the prevention of infection, with timely coverage of the defect. Although these lesions are known to heal with dressing changes, staged procedures may be necessary with tissue expansion and skull reconstruction.

32.5.4 Vascular Lesions of the Scalp

Vascular lesions of the scalp are common in children, occurring in up to 75% of all newborns.⁷³ The most common type appears as pink to red macular lesions over the forehead, face, or nuchal regions, and it usually fades completely over the first year or two of life. Some cutaneous vascular lesions actually progress with age. Cutaneous *hemangiomas* and cavernous malformations occur predominantly in the head and neck in newborns. They typically progress during the first year of life with spontaneous, often remarkable, involution thereafter.

So-called *port-wine stains* are dermal regions containing abnormal blood vessels, usually capillaries and venules within the superficial vascular plexus.⁷³ Port-wine stains may become increasingly conspicuous with progressive deformity of the soft tissues and occasionally the underlying bone. This process appears to result from progressive ectasia of the involved vessels rather than vessel proliferation. A deficiency of normal sympathetic innervation of the involved vessels may be causative.⁷⁴

From a neurosurgical point of view, port-wine stains of the scalp and face may be markers of underlying cerebral

involvement. Five percent of patients with port-wine stains have Sturge-Weber syndrome, with abnormal pial vasculature of the ipsilateral cerebral cortex, seizures, and varying degrees of cognitive impairment.⁷³ Treatment of the cutaneous lesions is usually by argon or tunable dye laser irradiation and is dependent on cosmetic and psychological concerns in young children.⁷³

32.5.5 Arteriovenous Malformations of the Scalp

Fistulous arteriovenous communications may occur in the scalp and appear as pulsatile, compressible masses or with high-output heart failure in infants. These scalp arteriovenous malformations (AVMs) are frequently referred to as cirroid aneurysms of the scalp.⁷⁵ Most scalp AVMs, especially in children, appear to be congenital; however, up to one-third may be acquired after trauma.⁷⁶ In infants, the lesions may enlarge, thus consuming an increasing proportion of the cardiac output as well as creating marked venous dilatation throughout the scalp and face.

Contrast CT may show enhancement of the subgaleal scalp, and MR imaging with MR angiography may further demonstrate the malformation, but catheter angiography is necessary to delineate the vascular anatomy clearly. CT angiography in children should be carefully considered because of the radiation exposure. Arterial feeding and venous draining vessels are predominantly extracranial; however, a small contribution may be demonstrated from “parasitized” intracranial vessels with compression of the extracranial arterial supply.⁷⁶

The direct surgical treatment of AVMs of the scalp may be exasperating, with significant blood loss intraoperatively and an unexpectedly high recurrence rate postoperatively.⁷⁶ Modern endovascular techniques of either direct puncture or transarterial embolization with a variety of thrombogenic agents can significantly reduce blood flow or even obliterate these malformations.^{75–79} Surgery is often required to resect residual fistulas or to remove the mass of embolic material.^{75,78} Apart from blood loss, the most significant surgical complication is scalp necrosis.⁷⁶ Care must be taken not to carry the epigaleal dissection into the hair follicles of the scalp. The scalp incision should be planned based on the anatomy of the AVM as well as on the possible need for scalp flap rotation.

32.5.6 Sinus Pericranii

In contrast to scalp AVMs, the vascular lesion referred to as *sinus pericranii* is a relatively slow-flow anastomosis between extracranial and intracranial veins, usually involving the superior sagittal sinus.⁸⁰ The lesion presents as a painless swelling of the scalp, usually in the midline or para-midline. The lesion is compressible, deflates with head elevation, and refills with Valsalva maneuver or with the head in a dependent position. Like scalp AVMs, most sinus pericranii lesions appear to be congenital, although some may be posttraumatic. Sinus pericranii presents predominantly in childhood but may come to medical attention during adulthood, especially when acquired after trauma.

In most cases, sinus pericranii can be diagnosed clinically. Skull X-rays show only the skull defect, which may be quite

small. Contrast CT and conventional angiography frequently fail to adequately illustrate the lesions. Direct injection of contrast into the blood-filled subgaleal mass may be required if radiographic confirmation is desired.^{80,81} Sinus pericranii is usually adequately treated by direct surgical obliteration without preoperative embolization. The decision to operate is based on symptoms, cosmetic concerns, and fear of bleeding from the lesion, the perceived risk of which is usually greater than the actuality.⁸⁰

32.6 Lesions of the Skull

A wide variety of bone lesions present in childhood, including developmental, inflammatory, traumatic, and both benign and malignant neoplastic pathologies. Mostly, these lesions occur in the extracalvarial skeleton, with only sporadic appearances in the skull. The list of lesions is extensive, and only those pathologies with significant presence in the skull are reviewed here. The interested reader is referred to the more general reviews of bone tumors in children.^{82,83}

32.6.1 Epidermoid and Dermoid Cysts

Dermoid and epidermoid cysts are the most common lesion of the scalp and calvaria encountered by pediatric neurosurgeons; they account for about half of masses in this region.^{3,4} Dermoid cysts and dermal tracts are more likely to present in the scalp and skull of young children, whereas epidermoids tend to occur intracranially in older children and young adults. These congenital lesions are thought to result from varying degrees of failure of disjunction of neuroectoderm from cutaneous ectoderm during closure of the neural tube.

Dermoid cysts contain elements of full-thickness skin, including epithelium, hair structures, and sebaceous glands. There may or may not be a visible sinus or pit overlying the lesion. The lesions are usually first observed by the parents in the newborn period. Occasionally, a small cyst may enlarge or become infected, prompting evaluation. Growth occurs as epithelial cells desquamate and break down, producing an accumulation of keratin and cholesterol. The most common location in children is at the anterior fontanel, where there is rarely dural penetration.⁸⁴ Many experienced surgeons forego neuroimaging of lesions in this location except in unusual situations. Dermoid cysts also occur along sutures, usually without dural penetration. However, dermoid cysts of the occipital midline often have some degree of intracranial involvement, and MR imaging is recommended.¹⁰ MR images should be obtained with diffusion weighting, which reveals restricted diffusion (► Fig. 32.1c). Even when neuroimages fail to show intracranial penetration, exploration frequently shows a slender tract extending through the cranial bone and attaching to the dura. In these cases, the tract may simply be coagulated and divided, and intradural exploration is usually not indicated because of the relationship to midline dural venous sinuses.¹⁰

32.6.2 Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is an abnormal proliferation of cells similar to Langerhans cells normally found in skin and

lymph nodes.⁸⁵ Although the proliferations are clonal, current thinking regarding etiology is shifting from neoplasia to defective immune regulation.⁸⁶ An inciting stimulus is as yet unidentified. LCH has an incidence of 8 to 9 per million per year in children.⁸⁶ In the past, depending upon the extent of involvement, LCH was variously known as eosinophilic granuloma, Hand-Schüller-Christian disease, or Letterer-Siwe syndrome. In the aggregate, these forms were also known as histiocytosis X. Langerhans cell histiocytosis is the current preferred terminology.

LCH usually appears before puberty, typically in children 4 to 12 years of age.⁸⁷⁻⁸⁹ The clinical presentation of LCH is extremely variable. Most bones and virtually any organ, including the brain, may be affected.^{88,89} Risk is based on classification into single-system LCH and multisystem LCH (Minkov). Single-system disease may be uni- or multifocal. The most frequent site of involvement is the skull; the child typically presents with a painful mass and often with a history of recent growth or antecedent trauma.⁹⁰ LCH of the skull base also occurs and may present more of a diagnostic dilemma. Temporal bone lesions can present with symptoms resembling those of otitis media or mastoiditis.⁹¹ Lesions of the clivus may present with abducens nerve palsies, which in children may appear as abnormal head position.⁹² Dural sinus thrombosis caused by compression from an occipital LCH lesion may lead to symptoms of pseudotumor cerebri.⁹³

Skull radiographs show a radiolucent, “punched-out” lesion without sclerotic margins (► Fig. 32.3a). CT of the skull defines intracranial extension, which is usually minimal (► Fig. 32.3b).⁹⁴ The lesion is characterized by low intensity on T1-weighted MR images and high intensity on T2-weighted MR images.⁹⁵ LCH lesions enhance markedly but inhomogeneously.⁹⁵ A tail of dural enhancement and enhancing reactive change in the overlying galea and muscle is a common finding not indicating invasion (► Fig. 32.3c).^{95,96}

Although unifocal involvement of the skull is common, it is important to rule out involvement at other sites. Multifocal bone involvement occurs in 28% of children and 20% of adults.⁸⁷ Radiographic skeletal survey and radionuclide bone scan appear to be complementary for the evaluation of polyostotic disease.⁹⁷⁻⁹⁹ Bone scan better detects lesions in the ribs and vertebrae, and skeletal X-rays are more accurate for the skull and long bones.⁹⁷ Cerebral involvement is often heralded by diabetes insipidus, and hypothalamic lesions may be seen on MR imaging.^{99,100}

The treatment of unifocal LCH of the skull usually consists of complete, full-thickness excision of the lesion.¹⁰¹⁻¹⁰³ There is rarely underlying dural penetration. Reconstruction of the defect with autologous split-thickness cranial bone from adjacent skull is easily performed at the time of primary resection. Biopsy and curettage have been recommended, but without clean bone margins, the healing of a bone graft may be impaired. Complete resection is associated with a low recurrence rate, and adjuvant treatment is not usually indicated.¹⁰¹⁻¹⁰³ Although surgical treatment is generally undertaken, spontaneous resolution of skull lesions has also been documented.¹⁰⁴ Thus, some authors recommend a period of observation to see if spontaneous resolution occurs.^{87,89,104} Enthusiasm for conservative management may be tempered by the possibility of hemorrhagic complications arising from cranial LCH lesions.^{105,106} It is also

unclear if persistent lesions predispose to disseminated disease.^{107,108} Recently, LCH in the orbit, mastoid, or temporal skull region has been classified as “central nervous system risk” because of an increased frequency for the development of diabetes insipidus and other endocrine abnormalities or parenchymal brain lesions.¹⁰⁹

Surgery for LCH of the long bones is often avoided because of the risk for instability. Thus, there is more experience with the nonsurgical management of lesions in these locations. Success has been demonstrated for local steroid injection¹⁰⁸ and for a wide variety of systemic therapies and low-dose radiation therapy.⁸⁶

Disseminated or multisystem involvement, patient age younger than 2 years at diagnosis, and hepatosplenomegaly or thrombocytopenia are poor prognostic factors.^{87,89} Recurrent or progressive disease may be treated with low-dose radiation or chemotherapy. Stereotactic radiotherapy may prove beneficial for focal skull base lesions.⁵⁰ Chemotherapeutic regimens for high-risk patients are actively being developed.^{109,110}

In keeping with the unknown etiology of LCH, the natural history of the disease is also not clearly understood; likewise, the influence of current therapeutic modalities is not well defined. Surgery, radiation, and chemotherapy have not been shown conclusively to affect outcome. The reported occurrence of new bone lesions in children is 22%, and the local recurrence rate after treatment is 6%.⁸⁷ Recurrence is usually seen within 2 years of the diagnosis; in adults, recurrence may be years later.⁸⁷ It seems reasonable to follow children with LCH of the skull for at least 5 years with X-rays, bone scans, or both. Fortunately, recurrent or new bone lesions without extraskeletal involvement are not associated with a worsened prognosis.^{87,109,111}

32.6.3 Aneurysmal Bone Cysts

Aneurysmal bone cysts (ABCs) are tumorlike expansions of the diploic space that distort and attenuate the overlying cortical bone (► Fig. 32.42). The cystic lesions themselves are filled with blood and lined by connective tissue with giant cells and trabecular bone.¹¹² About 80% of these lesions come to medical attention before the end of the second decade of life.^{112,113} Only 2% of ABCs arise in the bones of the skull.¹¹⁴ Up to 30% may involve the spine (Novais). Most experience with ABCs has been obtained with lesions in the long bones. Of skull lesions, about two-thirds are confined to the maxilla or mandible.¹¹⁴ Presentation in the skull usually involves a painful expanding mass.¹¹⁵ Cranial neuropathies may be present if the lesion is in proximity to the cranial nerve foramina.¹¹⁶ These tumors may grow to considerable size, especially in infants, and may present with raised intracranial pressure.^{117,118}

Although the etiology of ABCs is not known, nearly one-third of the lesions in the long bones are considered “secondary” to other bone lesions, such as giant cell tumors and osteoblastomas.^{112,113} A similar association has been observed in ABCs of the skull⁶⁷ with additional primary pathologies, including LCH and fibrous dysplasia.¹¹⁷⁻¹¹⁹ Thus, although the radiographic appearance of these lesions may be characteristic, a diligent pathologic search must be made for any accompanying lesion.

ABCs have a distinctive radiographic appearance, with expansion but not destruction of the cortical bone and fluid-fluid levels within the cysts themselves (► Fig. 32.2e). Although they

may expand intracranially, they do not penetrate dura. ABCs are vascular lesions, and direct operation in children is frequently associated with significant blood loss. Preoperative angiography is thus often indicated, with the consideration of embolization.

Treatment is usually surgical, after embolization. Complete resection is the goal, followed by primary reconstruction. Curettage of residual abnormal bone along margins that are not safely resected is acceptable. However, in long bones, curettage alone is associated with a recurrence rate of up to 60%.¹¹³ For this reason, and considering the association of ABCs with other bone lesions, close postoperative radiographic surveillance is recommended. Residual or recurrent lesions usually respond to radiation therapy, with its inherent risks.¹¹³ Cryosurgery reduces rates of recurrence after primary surgery and offers an alternative to radiation therapy when recurrent disease is treated.¹¹³ However, application in the cranium has not yet been reported. In cases in which the risk of operative resection is considered too great, the direct injection of acrylic sclerosing agents has been reported to be effective.¹²⁰

32.6.4 Osteoma, Osteoblastoma, and Osteoid Osteoma

Osteomas are seen mostly in young adults and rarely in children.^{121,122} They arise from mature cortical bone and have a distinctive CT appearance of a hyperdense, expansile lesion without bony destruction. MR imaging is variable in these tumors and thus of limited use.¹²³ If the lesion is asymptomatic and without cosmetic significance, observation is acceptable. It is not known whether simply drilling these lesions to achieve a normal contour is associated with a significant rate of recurrence. We prefer complete resection and repair with a split-thickness cranial bone graft, for which the recurrence rate is low.¹²²

By contrast, osteoblastoma occurs more frequently in children.¹²⁴ Despite the ominous suffix, osteoblastoma in children is usually considered benign.^{124,125} It accounts for approximately 1% of benign bone tumors, and 10 to 20% of all osteoblastomas occur in the skull.¹²⁶ Histologically, osteoblastoma is composed of immature osteoid material laced with osteoblasts. The appearance is similar to that of osteoid osteoma, but more variable calcification is seen within the lesion. Because of the variable calcification pattern, radiographs and CT may fail to render the correct diagnosis.¹²⁵ Although histologically benign, osteoblastomas may enlarge and are frequently painful. Complete full-thickness resection is recommended.^{124,125} In older patients, osteoblastomas may have a more malignant appearance with features of low-grade osteosarcoma.^{122,127}

Osteoid osteomas may occur in any bone but are quite rare in the skull.¹²² The average age at presentation is 19 years, and the lesions are painful in the majority of cases.¹²² The pain classically is dull and throbbing, more severe at night, and relieved by aspirin. The recurrence rate after complete resection is low.¹²²

32.6.5 Fibrous Dysplasia

Fibrous dysplasia is a benign disease in which normal bone is replaced by slowly growing fibro-osseous tissue. The abnormal tissue is composed of fibroblasts and collagen interspersed with

immature woven bone.¹²⁸ The process begins within the medullary cavity of the affected bone and expands, thinning and distorting the cortical bone.¹²⁹ Involvement may be confined to a single bone (monostotic) or include multiple, usually contiguous bones (polyostotic). As the area of dysplasia grows, the dysplasia appears to be able to cross suture lines into adjacent bones.¹³⁰ This type of polyostotic disease is particularly frequent in the craniofacial skeleton and therefore warrants the attention of craniofacial surgeons and neurosurgeons.

Polyostotic fibrous dysplasia may occur with precocious puberty or other hypersecretory endocrinopathies—most frequently involving growth hormone, thyroid hormone, or cortisol. This association is part of the *McCune-Albright syndrome*, which may also include café au lait hyperpigmented skin lesions. Fibrous dysplasia and McCune-Albright syndrome together may represent a spectrum of disease resulting from the abnormal expression of a subtype of G proteins.¹²⁹

Fibrous dysplasia accounts for approximately 2.5% of all bone tumors.¹³¹ It appears most commonly around puberty and is distributed equally between the sexes. Although disease activity is greatest before skeletal maturation, presentation or progression may occur well into adulthood.¹³² Although progression is usually slow, more acute changes in size can occur with cystic degeneration, hemorrhage, or the unusual association of fibrous dysplasia with ABCs. Involvement of the skull occurs in up to 27% of patients with monostotic fibrous dysplasia and 50% of patients with polyostotic fibrous dysplasia.^{133–135}

The initial presentation usually involves a history of painless, progressive deformity of the skull.¹³⁰ When the orbit is involved, there may be displacement of the globe with proptosis and diplopia. The changes often occur so gradually that diplopia is unnoticed by the patient. With involvement of the bones of the skull base, the cranial nerve foramina may become narrowed. The most common cranial neuropathy results from narrowing of the optic canal. Decreased visual acuity may occur gradually or acutely.^{135–137} Temporal bone involvement may result in tinnitus, hearing loss, facial palsy, and temporomandibular joint restriction.¹³⁸

Fibrous dysplasia is best imaged with thin-section CT in the coronal and axial planes. The diagnosis is usually apparent by the CT findings of expansion of the involved bone with a “ground glass” appearance. MR imaging may be useful to evaluate intracranial extension or the relation of cranial nerves to the lesion. A grading system dividing the skull into four zones has been devised to assist with operative planning.¹³⁹

Depending on the degree of involvement, the surgical goal should be complete resection with primary reconstruction. If the entire lesion cannot be completely resected, as is frequently the case with expansion into the central cranial base, subtotal resection with decompression of the involved neural foramina should be performed. Progression of residual disease once the bulk of the lesion has been removed usually does not occur.^{130, 139} Furthermore, autologous cranial bone grafts appear to heal well and are not infiltrated by the dysplastic process when placed in proximity to residual involved bone.^{130,139} Another option is to autoclave and replace bone that would be difficult to reconstruct. Over time, this treated bone has been shown to be replaced by normal bone.¹⁴⁰ Reconstruction with dysplastic bone has even been reported, with reasonable long-term results.¹⁴¹

The issue of optic canal involvement in the setting of fibrous dysplasia deserves special consideration. Previous enthusiasm for optic nerve decompression was based on the assumption that visual loss is a result of progressive compression of the optic nerve by a stenotic optic foramen. Decompressions have been performed prophylactically as well as therapeutically for both chronic and acute visual loss. However, visual loss can occur from prophylactic decompression.¹⁴² It has more recently been postulated that the visual loss in fibrous dysplasia is multifactorial, resulting from cystic fibrous dysplasia, mucocoeles, and hemorrhage, as well as longitudinal traction on the optic nerve by bony displacement of the orbit.¹⁴³⁻¹⁴⁶ In addition, visual loss has not been correlated with the degree of optic foramen stenosis and is not necessarily progressive.¹⁴⁶ A recent meta-analysis of 27 studies examined the issue of optic nerve compression in the setting of fibrous dysplasia.¹⁴⁷ In this study, the authors reviewed a total of 368 optic nerves affected by fibrous dysplasia. All clinically impaired nerves underwent decompression, with an improvement in visual function in 67.4%. Of the clinically intact nerves, 15% were decompressed prophylactically, while the others were followed expectantly. Surgery in asymptomatic patients was associated with visual deterioration, with long-term stable vision noted in 75.6% compared with 95.1% of the nonoperated nerves. This study adds to the mounting experience that prophylactic decompression is unlikely to be beneficial in the long term. Therapeutic decompression, conversely, remains a viable option. In our experience, an extradural approach is effective and can be performed with good results and minimal morbidity. The distorted anatomy can be daunting, and when identified, the superior orbital fissure is a useful surgical landmark. Image guidance systems can be reassuring in complex cases. Physical models are helpful in conceptualizing and identifying the involved anatomy.

The goals of surgery are generally to correct cosmetic deformities and to improve or stabilize neurologic dysfunction. Additional benefit, however, may be derived from the prevention of recurrence or malignant transformation.¹³⁹ It is estimated that in approximately 0.5% of patients with fibrous dysplasia, the fibrous dysplasia undergoes malignant degeneration, usually to osteosarcoma.^{128,148} The role of radiation in this process is not entirely clear, but it may predispose to malignancy.¹⁴⁹ Therefore, radiation therapy is not recommended in patients with primary or residual fibrous dysplasia.

Other fibrous bone lesions occur in childhood but rarely involve the skull. Ossifying fibroma, also called osteofibrous dysplasia, and nonossifying fibroma are both uncommon in the skull. When present in this location, they generally involve the facial skeleton more than the cranial vault. Because of this rarity, when these lesions occur in the cranial vault they typically warrant biopsy and resection for cosmetic and functional indications.¹⁵⁰

32.6.6 Malignant Skull Tumors

As in adults, malignancies of the skull in children are usually metastatic. The histologies of these lesions are characteristic for each pediatric age group. Thus, in children with skull tumors demonstrating radiographic signs of malignancy, further studies in search of the primary source must be considered.⁸²

Small skull metastases of a known primary are usually treated with radiation or systemic chemotherapy without neurosurgical involvement. The attention of the neurosurgeon is sought when neural compression is apparent or biopsy is indicated. The previously dismal prognosis of patients with these tumors has improved markedly over the last two decades, so that the complete resection of solitary lesions, as well as planning for subsequent reconstruction, has become a potentially more rewarding endeavor.¹⁵¹⁻¹⁵³

Melanotic neuroectodermal tumor of infancy (MNTI), also known as melanotic progonoma, is an uncommon tumor considered to be derived from the neural crest. It is unique in that the lesion is grossly pigmented and thus appears black or dark purple at surgery. A review of 335 cases showed that 61% occurred in the mandible, 16% in the calvaria, and 6% in the brain.¹⁵⁴ The vast majority (>90%) of patients present in the first year of life.¹⁵⁴ Although usually benign, the tumor typically exhibits a period of alarmingly rapid growth in infancy.¹⁵⁴ In the calvaria, these tumors can be quite large and may grow inward without resulting in external skull deformities.^{155,156} MNTI of the calvaria usually appears hyperdense on CT and may be confused with hyperostosis.^{157,158} MR imaging demonstrates T1 and T2 hypointensity and may show T1 shortening corresponding to tumor melanin content.¹⁵⁵ Total surgical removal is generally curative.^{154,159} The published recurrence rate of 20% is thought to represent inadequate excision.^{154,158} Malignant MNTI accounts for 6% of cases and is disproportionately associated with brain localization.¹⁵⁴

Sarcomas

Osteosarcoma (osteogenic sarcoma) and *Ewing sarcoma* are malignant bone tumors typically occurring in older children and young adults. They are usually found in the long bones but may metastasize to the skull. Osteogenic sarcoma and Ewing sarcoma as primary tumors of the skull are quite rare.¹⁶⁰⁻¹⁶⁴ Parosteal osteogenic sarcoma is a distinct surface bone tumor that, although rare in the skull, seems to have a better prognosis than conventional osteogenic sarcoma.¹⁶⁵ With long-term survival of patients with brain tumors, postradiation sarcomas have been reported within the field of radiation.¹⁶⁶

Sarcomas in the cranium usually appear as osteolytic lesions with poorly defined margins on X-ray and CT. They are aggressive lesions, and MR imaging often reveals infiltration of the surrounding soft tissues. At the time of diagnosis, intracranial extension is frequent, and patients may present with signs of raised intracranial pressure.^{165,167} These lesions are highly vascular, and MR angiography or conventional angiography may be valuable in preoperative planning, including the consideration of arterial embolization.

Treatment consists of as complete a surgical resection as possible, followed by chemotherapy and radiation as indicated by histology and institutional protocols. Preoperative MR imaging usually indicates whether intradural exploration will be necessary as these tumors may penetrate the dura and expand along the subdural space. In general, we make no attempt at the time of primary resection to reconstruct the calvaria because healing and immunocompetence will be inhibited by subsequent adjuvant therapy. The initial scalp incision should, however, take into account the possible need for cranioplasty in the future.

Neuroblastomas

Neuroblastoma is the most common extracranial solid tumor in children.¹⁶⁸ By virtue of the number of patients involved, it is therefore the most common tumor to metastasize to the skull in this age group. Skull metastases may present as a swelling of the skull, and X-rays and CT demonstrate a lytic lesion with a characteristic “hair-on-end” appearance.¹⁶⁹ Cranial MR imaging is usually performed as part of the metastatic work-up, although intracranial metastases are rare. These metastases are rarely resected because the tumor is usually responsive to current chemotherapy regimens, depending on the clinical stage.¹⁶⁸ Operation may be indicated for biopsy of suspected recurrent disease or resection of apparently solitary disease after systemic therapy.

Leukemias and Lymphomas

Many of the various leukemias and lymphomas involve the bones of the cranium by virtue of bone marrow invasion.¹⁷⁰ Again, systemic therapy based upon histologic diagnosis and institutional protocols generally obviates the need for neurosurgical treatment.

Pearls

- Scalp and skull masses in children comprise a diverse collection of pathologic diagnoses. Congenital and inflammatory lesions are common.
- Most skull neoplasms in children are benign, and complete excision is curative.
- Patients with suspected LCH of the skull should be evaluated with skeletal radiographs for multifocal disease.
- Complete resection of fibrous dysplasia is not always necessary.
- Resection of scalp and skull lesions should be performed in anticipation of immediate or delayed reconstruction.

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33 Brain Tumors in the First Two Years of Life

Nelson Moussazadeh and Mark M. Souweidane

Brain tumors manifesting in children younger than 2 years comprise a unique realm of neuro-oncology. These lesions deserve separate consideration for several reasons, all of which can profoundly impact the eventual outcome of a very young patient. Their anatomical distribution strongly favors the supratentorial compartment, whereas a predilection for the posterior fossa is seen in tumors in older children. Because of this distribution, in combination with an immature neurocognitive status, their clinical presentation is manifested not so much with neurologic findings, but rather with behavioral patterns and macrocrania of a relatively protracted and insidious duration. As a result, these tumors can achieve inordinately large dimensions before coming to medical attention and even before a correct diagnosis. Some histologic variants are so unique as to be rare in children beyond infancy. Surgical considerations that directly influence surgical morbidity include a relatively small circulating blood volume, poor thermoregulation, and incomplete skull maturity. Intraoperative adjuncts, including cortical mapping and stereotactic guidance, are rarely possible. Lastly, the therapeutic strategy needs to be tailored because of the well-recognized inverse relationship between age and potential treatment toxicity. We detail these features in this chapter, with special emphasis on the recent advances that continue to support the concept of segregating the brain tumors of very young children as a separate clinical entity.

33.1 Terminology

Previous attempts have been made to categorize young children with brain tumors according to the time of tumor genesis. Boldrey et al in 1950 proposed a definition based upon the time of symptom onset. According to this classification, children were labeled as having congenital, neonatal, or infantile brain tumors if symptoms were detected at birth, before 2 months of age, and between 2 and 12 months of age, respectively.¹ Solitare and Krigman in 1964 recognized the deficiency in this strategy because of the potential discordance between tumor origin and symptom onset.² They thus proposed that tumors be considered “definitely congenital” if symptoms were present at birth, “probably congenital” if symptoms occurred within 1 week, and “possibly congenital” when symptom onset was between 1 and 4 weeks of life. These early attempts to subcategorize and label infantile brain tumors are problematic.

In this chapter, we do not attempt to further subcategorize brain tumors in children younger than 2 years, with the exception of those tumors that are definitely congenital (i.e., symptomatic at birth). To do so presupposes an understanding of biological growth rates for varying histologic subtypes of tumors. Although it is sometimes certain that a tumor originated in utero, it is impossible to determine the time of disease onset for most children. Additionally, with any of the subclassifications outlined above, the true incidence of congenital tumors is underestimated. Spontaneous abortions and stillbirths resulting from brain tumors, estimated to account for as many as 25% of all congenital brain tumors, would not be captured in the

forementioned classification system.^{3–5} Furthermore, tumors that arise during embryogenesis, but do not become symptomatic until after infancy, would also be labeled incorrectly.

33.2 Epidemiology

Following a period of increasing incidence of pediatric brain tumors and of cancer generally from the 1960s through the 1990s related to improved radiographic diagnostics and reporting, the rate then stabilized.^{6–9} Tumors diagnosed within the first 2 years of life account for a stable proportion of childhood brain tumors, estimated at 12 to 18%.^{10–14} Pediatric brain tumors occur at an estimated frequency of about 4 per 100,000 person-years.¹⁵ Congenital brain tumors present at the time of birth or found in stillborns are relatively infrequent. Among all newborn and stillborn children diagnosed with cancer, brain tumors account for fewer than 5% cases, with a frequency of about 1.1 per 100,000 births.^{5,16} Most studies indicate a relatively equal distribution between the sexes for all tumors in aggregate, although some histologic subtypes, specifically medulloblastoma, continue to be more common in boys.^{4,17–20}

Although they account for a small proportion of children with brain tumors, infants with brain tumors afford valuable opportunities to better understand oncogenesis. That the brain tumors encountered in infancy manifest so early, with many encountered subtypes seen exclusively in this age group, suggests a strong contributory role of germline and embryonic abnormalities, and potentially fewer contributory postnatal mutational and epigenetic events. Compared with other tumors known to originate embryonically, the relatively short interval to disease symptomatology for these tumors suggests either universal penetrance with inevitable tumorigenesis or, alternatively, a scenario of high penetrance in which required Knudson “second-hit” insults are more common, are uniquely encountered, or are exclusively carcinogenic in this time period.

Genetic predisposition has been clearly established in several congenital brain tumor syndromes. For the most part, these syndromes are transmitted as autosomal-dominant traits despite the frequent harboring of mutations in tumor suppressor genes. Thus, most tumors possess biallelic loss of function manifesting as tumorigenesis. ▶ Table 33.1 summarizes the genetic locus, the gene product, and the most common type of brain tumor associated with each syndrome. What is clear from a rapidly expanding list of congenital syndromes with known genetic bases is the fact that primary brain tumors not appearing to arise by chance alone are frequently associated with a genetic predisposition to oncogenesis or mutagenesis that readily manifests systemically. However, in the absence of a recognized congenital syndrome, it currently remains inadvisable to recommend screening of the siblings or other first-degree relatives of young children with brain tumors.

Epidemiologic studies have rarely identified factors that are causally related to brain tumors in children. A multitude of potential causes have been investigated, with highly variable results and commonly contradictory conclusions. What is not

Table 33.1 Brain tumor syndromes and genetic basis

Genetic syndrome	Gene (locus)	Gene product	CNS tumor type	Inheritance
Neurofibromatosis type 1	<i>NF1</i> (17q11.2)	Neurofibromin 1	Pilocytic astrocytoma, neurofibroma, meningioma	AD
Neurofibromatosis type 2	<i>NF2</i> (22q12.2)	Merlin, neurofibromin 2	Vestibular schwannoma, meningioma, ependymoma	AD
Tuberous sclerosis complex (Bourneville disease)	<i>TSC1</i> (9q34) and <i>TSC2</i> (16p13.3)	Hamartin (<i>TSC1</i>), tuberin (<i>TSC2</i>)	Subependymal giant cell astrocytoma	AD
von Hippel-Lindau disease	<i>VHL</i> (3p26-p25)	von Hippel-Lindau protein (pVHL)	Hemangioblastoma	AD
Retinoblastoma	<i>RB1</i> (13q14.2)	Retinoblastoma protein (pRB)	Pineoblastoma	AD
Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	<i>PATCHED</i> (9q22.3)	PTCH	Medulloblastoma	AD
Cowden disease (multiple hamartoma syndrome)	<i>PTEN</i> (10q23.3)	PTEN	Dysplastic gangliocytoma (Lhermitte-Duclos disease)	AD
Turcot or familial adenomatous polyposis syndrome	<i>APC</i> (5q21-q22)	APC protein	Medulloblastoma, astrocytoma	AD
Li-Fraumeni syndrome	<i>TP53</i> (17p13.1)	p53 protein	Malignant astrocytoma	AD
Rhabdoid predisposition syndrome	<i>SMARCB1</i> , <i>hSNF5/INI1</i> (22q11.2)	INI1 protein	Atypical teratoid/ rhabdoid tumor, choroid plexus carcinoma	AD

Abbreviations: AD, autosomal-dominant; CNS, central nervous system; PTEN, phosphatase and tensin

debated is the finding that ionizing radiation has been established as a cause of primary brain tumors.^{21,22} The major causes of exposure have been traced to diagnostic and therapeutic medical radiation, environmental accidents, and combat-related sources. This risk from ionizing radiation is dose- and age-dependent, with increasing doses more contributory and younger children more susceptible. Much attention and investigation have been directed toward nonionizing radiation sources (including infrared, microwave, and nearly ubiquitous radio-frequency fields, including those emanating from mobile telecommunications devices), but no conclusive evidence supports causality. Inconclusive but suggestive evidence for causality does exist for maternal and paternal dietary ingestion of cured meats, the major dietary source of *N*-nitroso compounds.²³ The implication of parental exposure to polycyclic aromatic hydrocarbons, primarily through preconceptional smoking or occupational exposure, has historically been inconclusive, but the results of large contemporary or prospective studies suggest a relatively increased risk.^{24,25} Maternal exposure to viral infections during gestation has been reported to increase the odds of a central nervous system (CNS) tumor during childhood.²⁶ Debate continues, but no strong predictive values have been found for exposure to pesticides, petrochemical products, exhaust fumes, antihistamines, and a variety of other environmental agents.

33.3 Clinical Presentation

The ability of the infant skull to compensate for volume changes, the relatively increased cerebrospinal fluid (CSF) volume within the subarachnoid spaces and cisterns, a greater degree of extracellular fluid in the parenchymal compartment,

and early developmental status all affect the timing and mode of presentation of young children with brain tumors. In short, these features combine to result in a paucity of localizing neurologic signs, delayed clinical recognition, and generous tumor sizes. The most common presenting signs in this age group are thus manifestations of raised intracranial pressure, such as increasing head circumference, irritability, lethargy, emesis, and failure to thrive.^{14,17–20,27,28} Indeed, approximately 50 to 65% of children younger than 2 years of age with a newly diagnosed brain tumor present clinically with macrocrania with diastasis of the cranial sutures and tenseness of the fontanel. Similarly, seizures are relatively infrequent, occurring in only 10 to 15% of children at presentation. It is thus understandable that many of these children are initially diagnosed inaccurately and that the discovery of the brain tumor is quite delayed from the time of symptom onset. Most studies indicate an interval of about 8 to 12 weeks from symptom onset to diagnosis, with some reports indicating several months to years before the diagnosis was reached.

33.4 Anatomical Features

The topographic features of brain tumors in infants are distinct from those of older children. First, the relationship of tumor location to the tentorium is reversed in young children in comparison with children of older age groups. A summary of several large published series with a total of 1,252 cases indicates that in children younger than 2 years of age at diagnosis, supratentorial tumors account for 63.8% of lesions and infratentorial tumors are found in 32.4%.^{14,17–19,27–29} (► Fig. 33.1). If the age group is limited to children between birth and 2 months of age

Topography of Congenital Brain Tumors

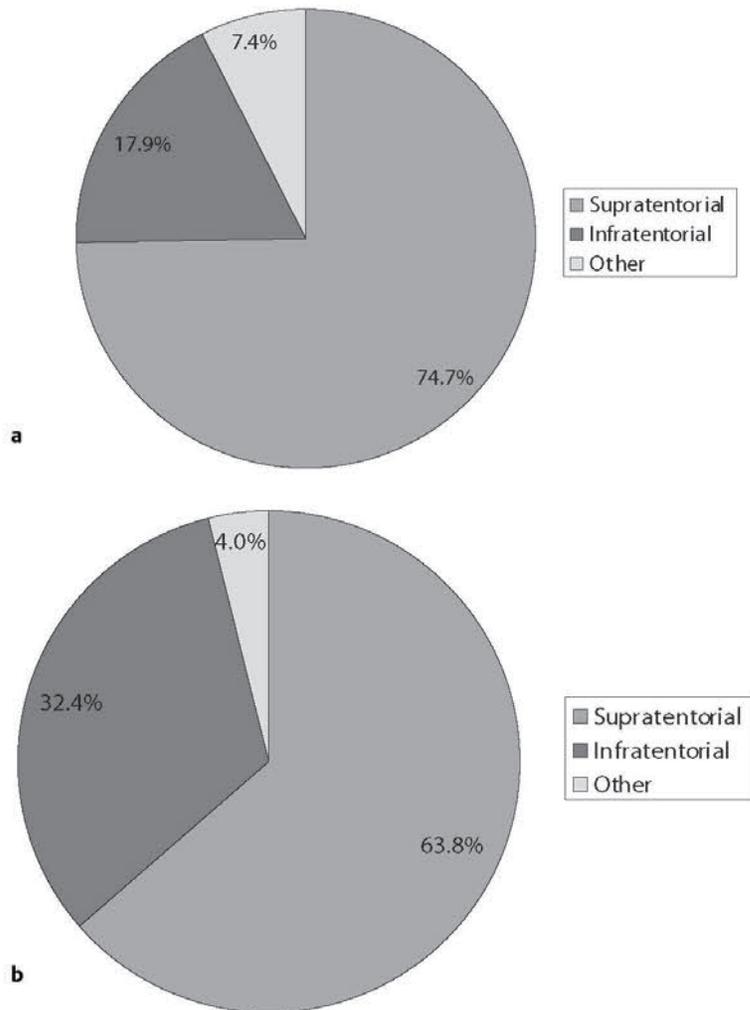


Fig. 33.1 Relative distributions of primary brain tumors in children in whom they are diagnosed before 2 years of age and in children in whom they are diagnosed at the time of birth (congenital).

at diagnosis, the distribution is further biased toward the supratentorial compartment, with 74.7% of tumors supratentorial and 17.9% located in the posterior fossa.^{3,32–34}

Another unique feature of brain tumors in very young children is their relatively large size. These tumors frequently occupy a significant portion of the hemispheric volume. In one series from The Hospital for Sick Children in Toronto, Ontario, Canada, the average maximal diameter of tumors in children younger than 1 year of age at diagnosis was 4.6 cm, with most tumors measuring between 4 and 10 cm in largest diameter.²⁰ Among 18 of 45 cases of congenital tumors reviewed in 1990 by Buetow et al, the tumor was noted to be “large, occupying more than one-third of the intracranial volume.”³² This finding was also noted by Tadmor et al in their 1980 treatise on children younger than 2 years of age with their comment that “...most of the tumors were extensive, involving more than one cerebral lobe.”²⁸ These tumors can also have characteristic cystic components that are distinct from loculate hydrocephalus. Some series indicate that the tumors of up to two-thirds of very young children have macroscopic cystic components.³² An example of these particular growth features is depicted in ► Fig. 33.2.

33.5 Tumor Types

The classification of brain tumors of infancy is based on the World Health Organization (WHO) system,³⁵ which classifies them principally according to the presumed cell of origin and degree of malignancy (grades I through IV). Although the classification system is universally used irrespective of patient age, several pathologic entities exist that remain unique to very young children and are rarely diagnosed in later childhood or adulthood. These specific tumors are found predominantly within the general categories of embryonal tumors, mixed neuronal–glial tumors, ependymal tumors, and choroid plexus tumors. Accurate diagnosis is reached through standard light microscopy, immunocytochemistry, and genetic analysis. Therefore, a detailed analysis of tumor tissue is crucial to establishing the correct diagnosis. It is clear from the experience in cooperative group studies using a central review process for pathologic interpretation that discordant diagnosis is not uncommon and potentially jeopardizes the validity of the outcome analysis.

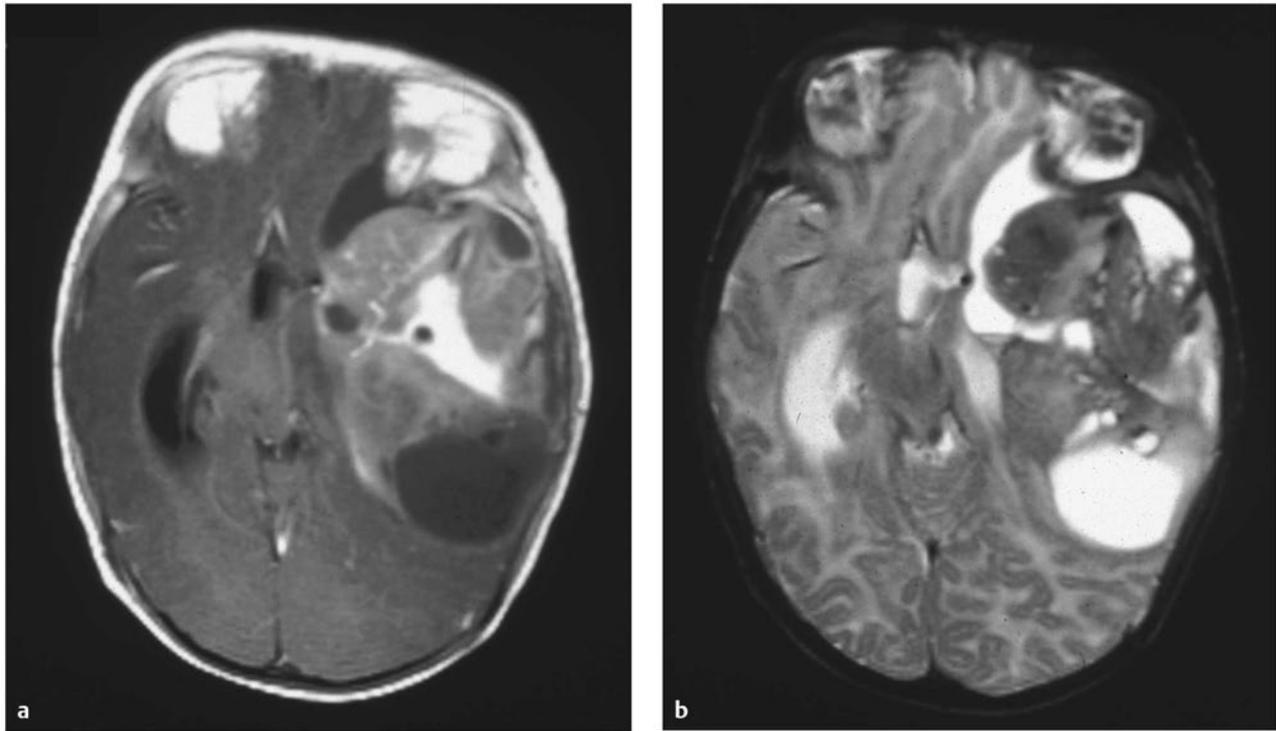


Fig. 33.2 Anaplastic astrocytoma. (a) Axial T1-weighted magnetic resonance image with contrast administration and (b) T2-weighted sequence in a 3-month-old boy who presented with failure to thrive and a divergent macrocrania. A very large mass with macroscopic cystic changes is seen in this anaplastic astrocytoma (World Health Organization grade III) of the left cerebral hemisphere. In addition to the severe mass effect, the tumor has caused ventriculomegaly, which accounts for a substantial component of the hemispheric volume.

As mentioned, the frequency of specific tumor types varies with age. The distribution of tumor types in children with a primary brain tumor who are younger than 2 years old at diagnosis is markedly different from the distribution of tumor types in older children. These relative frequencies for very young children are summarized by a review of published series cumulatively totaling 1,185 patients and are illustrated in ► Fig. 33.3.^{14,17–19,27–29}

Notably absent from these cumulative data and the large cancer registries is the atypical teratoid/rhabdoid tumor (AT/RT). The initial description of this rare tumor, accounting for approximately 1% of all pediatric brain tumors, occurred after most of the major publications pertaining to tumors in the very young had been published.³⁰ The majority of these tumors were most likely previously classified as primitive neuroectodermal tumor (PNET) or medulloblastoma in the period before 2000, when AT/RT was added to the WHO classification system.³⁶ In a French registry of pediatric brain tumors, 7 of 267 tumors in patients ages 0 to 4 years were AT/RT, versus 4 of 750 in patients ages 4 to 19 years.³¹ In an Austrian registry of pediatric WHO grade III or IV tumors, AT/RT accounted for 13 of 75 (17.3%) high-grade tumors in patients 0 to 2 years of age, versus 6 of 236 (2.5%) high-grade tumors in children ages 2 to 14 years.³⁷ The rate of diagnosis of AT/RT is significantly greater than that indicated in ► Fig. 33.3 and that indicated in large registries quantifying brain tumors in the first 2 years of life.

The major diagnostic categories of tumors in children younger than 2 years of age are described below. When appropriate, the

reader is referred to the corresponding chapter for that particular tumor. Here, we highlight the main features of each of the major histologic subtypes that are unique to infants and provide a more thorough assessment of the tumors that are particular to very young children and are seldom diagnosed beyond infancy.

33.6 Emerging Developmental Insights into Tumorigenesis

Oncogenesis has classically been understood to fundamentally represent the dysregulation of processes controlling cellular proliferation, longevity, and respect for surrounding tissues. A growing body of scholarship has established that co-opted processes of normal development frequently contribute to oncogenesis; indeed, in many tumor types, cancer stem cells embodying populations of aggressive cells capable of initiating or repopulating tumors harbor features of prematurity. Given their young age at presentation, it is therefore unsurprising that putative tumor cells of origin intimately associated with developmental progenitors have also been identified among CNS tumors of infancy.

The prototypical example of this is medulloblastoma of the cerebellum, a structure particularly susceptible to tumorigenesis because it undergoes a significant proportion of its development postnatally. Medulloblastoma comprises at least four subgroups that are biologically distinct on the basis of molecular signature, clinical behavior, and response to therapy; these include the sonic hedgehog (SHH), correlated with the

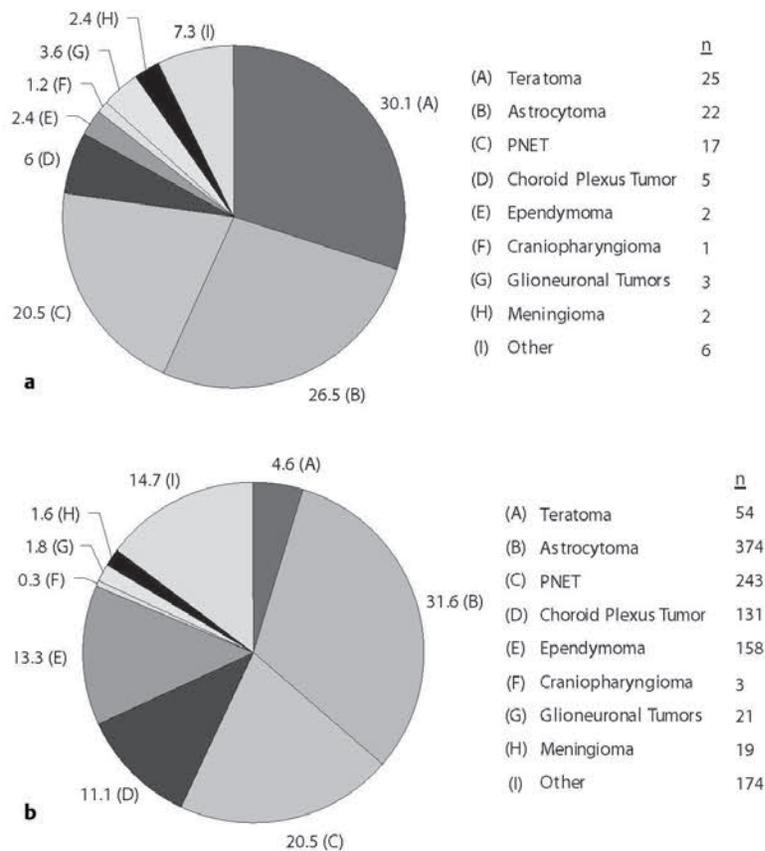


Fig. 33.3 Relative frequencies of tumor types in patients with tumors diagnosed (a) at the time of birth (congenital) or (b) within the first 2 years of life.

desmoplastic histologic variant), wingless (Wnt), and other “non-Wnt/non-SHH” genetic subtypes.³⁸ SHH-subgroup medulloblastoma, the most common subtype encountered in infants, has been shown to arise from cerebellar granule neuron progenitor cells. During normal development, granule neuron progenitor cells undergo massive expansion before cell cycle arrest and terminal differentiation in response to decreasing paracrine SHH as they migrate beyond SHH-secreting Purkinje cells en route to the internal germinal layer, where their quiescent progeny reside as granule neurons. In disease, this subgroup exhibits aberrant signaling of SHH, associated pathways including Notch, and downstream effectors of proliferation in addition to other oncogenic abnormalities.³⁹ Other cerebellar progenitors may similarly be responsible for medulloblastoma tumorigenesis, with recent evidence that those originating in the upper and lower rhombic lips may provide tumor cells of origin for some Wnt-subtype tumors.⁴⁰ These insights have already potentially yielded therapeutic targets such as hedgehog inhibitors, and advances in developmental and tumor biology may accelerate future prognostic and therapeutic progress.⁴¹

33.7 Primitive Neuroectodermal Tumors

33.7.1 Medulloblastoma

Medulloblastoma is the most common brain tumor in infants, accounting for nearly 50% of newly diagnosed brain tumors in

children younger than 2 years of age. Of all medulloblastomas diagnosed in children, 25 to 35% occur in children younger than 3 years of age.⁴² As expected, children with these tumors primarily present with symptoms of intracranial hypertension secondary to hydrocephalus resulting from fourth ventricular obstruction (► Fig. 33.4). Medulloblastomas tend to carry a worse prognosis in children younger than 2 to 3 years old. The cause of the unfavorable prognosis in this age range is speculated to result from the avoidance of radiation therapy, although some suggestion has been made that medulloblastoma in very young children may have a more aggressive biological behavior. Furthermore, leptomeningeal dissemination has been reported to be present in 27 to 43% of younger children, although this higher rate of metastatic spread is not found in all retrospective series.^{43–45}

The histopathologic grading of medulloblastoma indicates that some prognostic significance is achieved by subclassifying these tumors, although commonly used treatment regimens do not currently stratify patients on the basis of pathologic interpretation. The 2000 WHO classification recognized four separate varieties of medulloblastoma: classic medulloblastoma, desmoplastic medulloblastoma, large cell/anaplastic medulloblastoma (LC/A MB), and medulloblastoma with extensive nodularity (MBEN).⁴⁶ (For a detailed discussion of medulloblastoma, the reader is referred to Chapter 40.) The latter entity, MBEN, has only recently been defined and warrants separate consideration, given its predilection for very young children. MBEN, although rare and accounting for fewer than 5% of

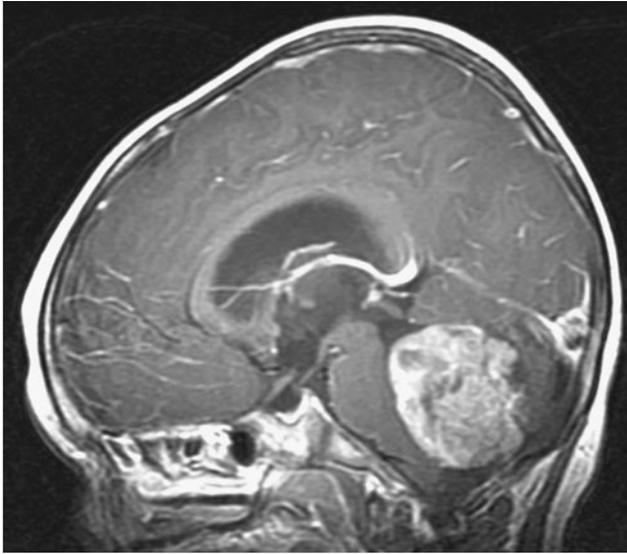


Fig. 33.4 Medulloblastoma. Sagittal magnetic resonance image following the administration of contrast in a 2-year-old boy presenting with macrocrania and intermittent morning vomiting. The fourth ventricular medulloblastoma and resulting noncommunicating hydrocephalus are easily seen on this preoperative image.

medulloblastomas, occurs most often in children younger than 3 years of age. This tumor, characterized by a cellular pattern of extensive nodular growth with strong neuronal differentiation, was formerly termed *cerebellar neuroblastoma* (► Fig. 33.5). This subtype of medulloblastoma has been shown to behave in a more indolent fashion; it metastasizes less frequently and carries a better prognosis than other medulloblastoma subtypes.⁴⁷⁻⁵⁰ However, given the challenges encountered in treating very young children and their resultant poor outcome, children younger than 3 years of age with medulloblastoma, irrespective of the extent of disease or presence of dissemination, are generally categorized as being at high risk.

The results of cooperative group studies show that the survival rates of very young children are significantly reduced compared with those of older children. The recent trend in treatment has focused on the attempt to avoid, delay, or reduce irradiation with chemotherapeutic supplementation. In a study of 12 children with medulloblastoma diagnosed before 3 years of age at MD Anderson Cancer Center in Houston, Texas, 8 children (67%) treated with chemotherapy alone had a median survival rate of 10.6 years.⁵¹ In 1993, the Pediatric Oncology Group (POG) reported a 5-year progression-free survival (PFS) rate of 32% and an overall survival (OS) rate of 40%.⁵² This study employed delayed radiation therapy (see below) and found complete surgical resection to be the strongest positive predictor. The Children's Cancer Group (CCG) employed "eight drugs in 1 day" for 46 children younger than 18 months and reported a 3-year PFS rate of 22%.⁴³ Subsequent studies by the CCG and Société Française d'Oncologie Pédiatrique (SFOP) employing conventional chemotherapy and reserving adjuvant radiotherapy for recurrent disease or as salvage treatment have borne similar outcome analyses for very young children with medulloblastoma: an expected approximately 30% PFS and approximately 40% OS at 5 years.^{53,54} Recent data published from the German

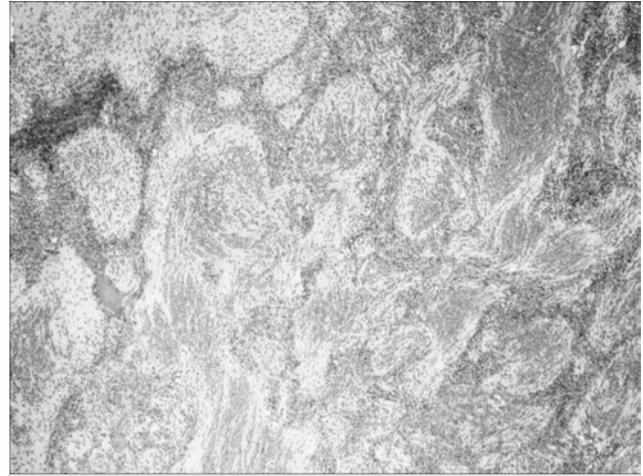


Fig. 33.5 Medulloblastoma. Low-power hematoxylin and eosin (H&E) stain of a medulloblastoma with extensive nodularity. This variant is characterized by a histologic phenotype having two major cytoarchitectural profiles. There are reticulin-free, synaptophysin-positive zones composed of well-differentiated neurocytes. These nodules are surrounded by reticulin-rich collagen regions with a subpopulation of poorly differentiated cells that do not stain for neuronal markers.

HIT-SKK87 registry noted approximately 50% and 60% PFS and OS at 10 years, respectively, in children younger than 3 years of age who were without either postoperative residual or macroscopic metastases at diagnosis and were treated with upfront adjuvant chemotherapy and craniospinal irradiation after age 3.⁵⁵

Other treatment regimens, including intensified chemotherapy and intrathecal routes of administration, have also been reported (see below). Of particular note, a recent study that utilized an intensive chemotherapeutic approach with intrathecal supplementation in children younger than 3 years of age reported favorable results.⁴²

Thus, children with medulloblastoma who are younger than 3 years of age at diagnosis are at a substantial disadvantage compared with older children in respect to overall outcome. The extent of surgical resection and degree of metastatic disease appear to influence outcome. Intensive chemotherapy and intrathecal routes are being used with increasing success to eliminate or reduce radiation exposure. Although histologic subtypes have not been effectively used to date in the prognosis or treatment of medulloblastoma, the recent description of molecular subtyping (including aberrant SHH signaling, most frequently seen in infants) and increasing knowledge of the cellular programs gone awry in the clinical syndrome will doubtless influence treatment goals, suggest avenues for drug design and delivery, and assist in tailoring therapy to an infant's individual disease.⁵⁶

33.7.2 Supratentorial Primitive Neuroectodermal Tumors

Long recognized as the hemispheric equivalent of the medulloblastoma, the supratentorial primitive neuroectodermal tumor (sPNET) clearly has a worse outcome than those

morphologically similar tumors of the cerebellum. These highly malignant neoplasms account for only 2.5 to 7% of childhood brain tumors, but they predominate in the very young.⁵⁷ In the infant population, these tumors can achieve very large dimensions and thus present an onerous challenge for surgical removal. In the 1995 summary of sPNETs from the CCG, 40% of the tumors had a maximal diameter of more than 6 cm; total resection was accomplished in only 37% of patients.⁵⁸ The POG review of sPNETs also reported the large dimensions of these tumors, with an average volume of 153.5 cm³.⁵⁹ In addition, these tumors frequently were found to involve more than one cerebral compartment, thus precluding the possibility of aggressive resection. As reported by the COG, the 5-year OS rate of 34% and PFS rate of 31% were statistically worse in children younger than 3 years at diagnosis.⁵⁸ In fact, that group showed a substantial reduction in the 3-year PFS rate from 53% for children younger than 3 years to 25% for children between the ages of 1.5 and 2 years old.⁶⁰

Some improvement in outcome has been purported with the use of dose intensification or high-dose chemotherapy and autologous bone marrow transplantation. Memorial Sloan-Kettering Cancer Center (MSKCC) reported a 2-year event-free survival (EFS) rate of 43% for 14 patients.⁶¹ In that particular series, however, 50% of the patients were older than 30 months of age at diagnosis, pineoblastoma was grouped together with sPNET, and there was a 6% treatment-related mortality rate. Among infants enrolled in the German HIT-SKK87 and SKK92 registries (ages 37 months or younger), the benefit of radiation therapy was of a magnitude (28.6% OS and 24.1% PFS among those treated with radiotherapy vs. 6.7% OS and PFS at 3 years among those with adjuvant chemotherapy alone) that prompted the authors to recommend that radiation be delayed by no longer than 6 months; however, this approach remains uncommon.⁶²

33.7.3 Pineoblastoma

PNETs of the pineal region, or pineoblastomas, are malignant embryonal tumors that arise from the pineal parenchymal cells (► Fig. 33.6). For the most part, pineoblastomas are histologically indistinguishable from PNETs in other locations. Their

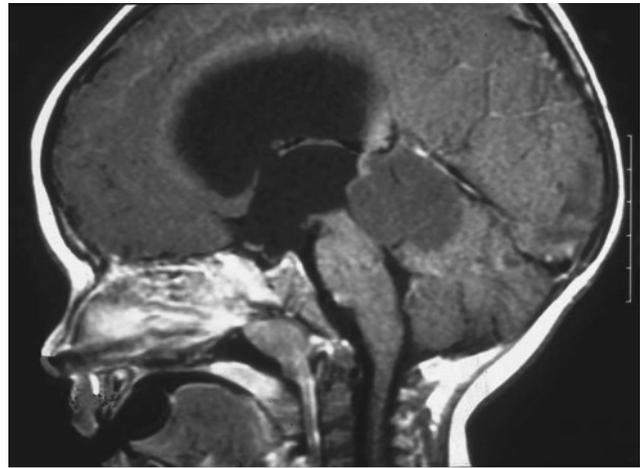


Fig. 33.6 Pineoblastoma. Sagittal magnetic resonance image following contrast administration in a 1-year-old boy who presented with macrocrania and vomiting. The lesion in the pineal region has obliterated the normal anatomical structures, causing obstruction at the level of the aqueduct and severe hydrocephalus. Histologic samples following total resection were indicative of a pineoblastoma (primitive neuroectodermal tumor of the pineal region).

behavior has been difficult to define, given the tendency to group this entity together with other malignant neoplasms of the pineal region, the historical therapeutic approach of using empiric radiation therapy, and the inaccurate assignment of the tumors to other histologic categories.

A very young child with a pineoblastoma has a significantly poor prognosis. Although justified, withholding irradiation is the most probable reason. The 1995 report by the CCG indicated widely disparate outcomes for children with pineoblastoma depending upon age at the time of diagnosis. The 3-year EFS rate for children younger than 18 months of age treated with chemotherapy alone was 0%, compared with a 3-year EFS rate of 61% for older children treated with combined radiation therapy and chemotherapy (► Table 33.2).⁶³ In the infant population, the median time to disease recurrence was 4 months, and the median time to death was 10 months. The POG reported

Table 33.2 Neoadjuvant chemotherapy for choroid plexus carcinoma^a

Author (year)	Patients	Chemotherapy regimen	Response
St. Clair et al (1991–1992)	4	Etoposide/ifosfamide/ carboplatin	4 PR
Packer et al (1992) ⁹⁴	1	Cyclophosphamide/vincristine	1 PD
Allen et al (1992) ⁹⁹	3	Etoposide/cisplatin	2 PR, 1 SD
Arico et al (1994)	1	Teniposide/procarbazine/intrathecal methotrexate/vincristine/ lomustine	1 SD
Duffner et al (1995)	4	Vincristine/cyclophosphamide	2 PR, 2 SD
Razzaq and Cohen (1997) ⁹⁷	1	Etoposide/ifosfamide/ carboplatin	1 PR
Total	14		9 PR, 4 SD, 1 PD

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

^aIncludes only patients with measurable disease following subtotal surgical resection or biopsy.

similarly dismal results in 11 infants with pineoblastoma when an approach of postoperative chemotherapy with the intent to delay radiation therapy was used. All patients failed chemotherapy, no patients had a response of their leptomeningeal disease, no children were salvaged with radiation therapy, and all children died of disease between 4 and 13 months from the time of diagnosis.⁶⁴

The use of high-dose chemotherapy with autologous stem cell rescue is being considered as the primary approach in young children with pineoblastoma, given the extremely poor rates of response to conventional chemotherapy without irradiation. No large cooperative study using such an approach for infants with pineoblastoma has been completed, but pilot study data indicate its feasibility. Of 13 patients with pineoblastoma recently treated at Duke University with high-dose chemotherapy and autologous stem cell rescue, two were younger than 1 year at the time of treatment.⁶⁵ These two patients, who had localized disease and underwent a complete surgical removal, had a continuous complete remission of 35 and 125 months' duration after treatment.

33.7.4 Trilateral Retinoblastoma

Trilateral retinoblastoma is a unique and particular tumor syndrome of infancy. This entity is defined as the composite of a previous history of bilateral retinoblastoma with a subsequent diagnosis of an intracranial PNET (► Fig. 33.7). Although subsequent intracranial PNET has been recognized in children with unilateral retinoblastoma, this is the rare exception. The overall incidence of an intracranial PNET, typically a pineoblastoma, in the presence of bilateral retinoblastoma is 2 to 11%.⁶⁶ The mean age of a child at the time of presentation with an intracranial tumor is about 24 months. In most reports, trilateral retinoblas-

toma has been uniformly fatal, with a mean length of survival after discovery of the intracranial tumor of 1.3 months for untreated patients and 9.7 months for treated patients.⁶⁷ The very poor outlook is partly due to the fact that up to 25% of patients have disseminated disease when the intracranial tumor is discovered. There is some evidence to support the use of neoadjuvant intravenous chemotherapy (chemoreduction) in children with bilateral retinoblastoma or a family history of retinoblastoma to reduce the incidence of trilateral retinoblastoma (► Table 33.2).⁶⁸

33.8 Ependymoma

Ependymoma of childhood is a rare tumor with an incidence of 2.1 to 2.5 per 1 million children younger than 15 years.⁶⁹ (The reader is referred to Chapter 41 for a complete discussion of ependymoma of childhood.) With a median age at onset in most large series between 36 and 52 months, the infant population represents a disproportionate fraction of children affected.^{70,71} In children younger than 2 years, the majority of these tumors are fourth ventricular in location. Ependymomas in infants are found less frequently in the supratentorial compartment, where they may be entirely intraparenchymal and have no relationship to the ventricular compartment. Those tumors arising within the cerebral hemispheres can attain voluminous sizes due to their relatively indolent growth rates (► Fig. 33.8).

A young age at the time of diagnosis has been repeatedly shown to negatively affect outcome in children with intracranial ependymoma. Proposed reasons include a lower rate of complete resection, the avoidance of radiation therapy, and biologically aggressive behavior.^{70,72} The outcome for infants

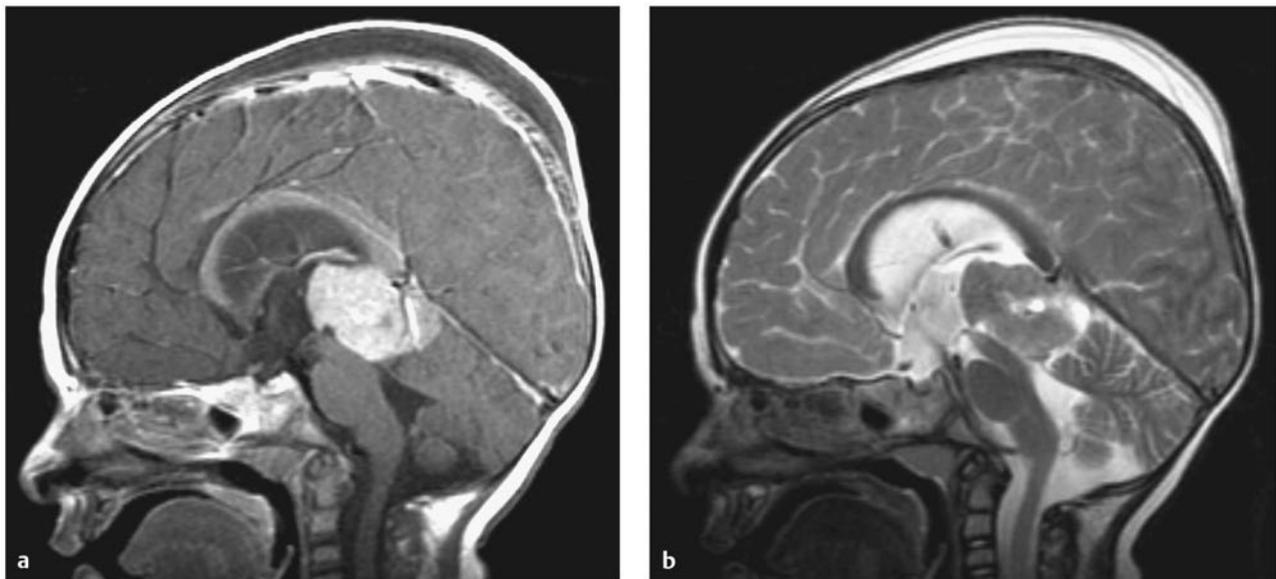


Fig. 33.7 Trilateral retinoblastoma. (a) Sagittal T1-weighted magnetic resonance image with contrast and (b) the corresponding T2-weighted sequence of an 11-month old girl previously treated for congenital bilateral retinoblastoma. The images were obtained after an endoscopic third ventriculostomy and tumor biopsy (note the turbulent flow pattern at the site of the third ventriculostomy). This child with trilateral retinoblastoma underwent total resection of a pineoblastoma following induction chemotherapy.

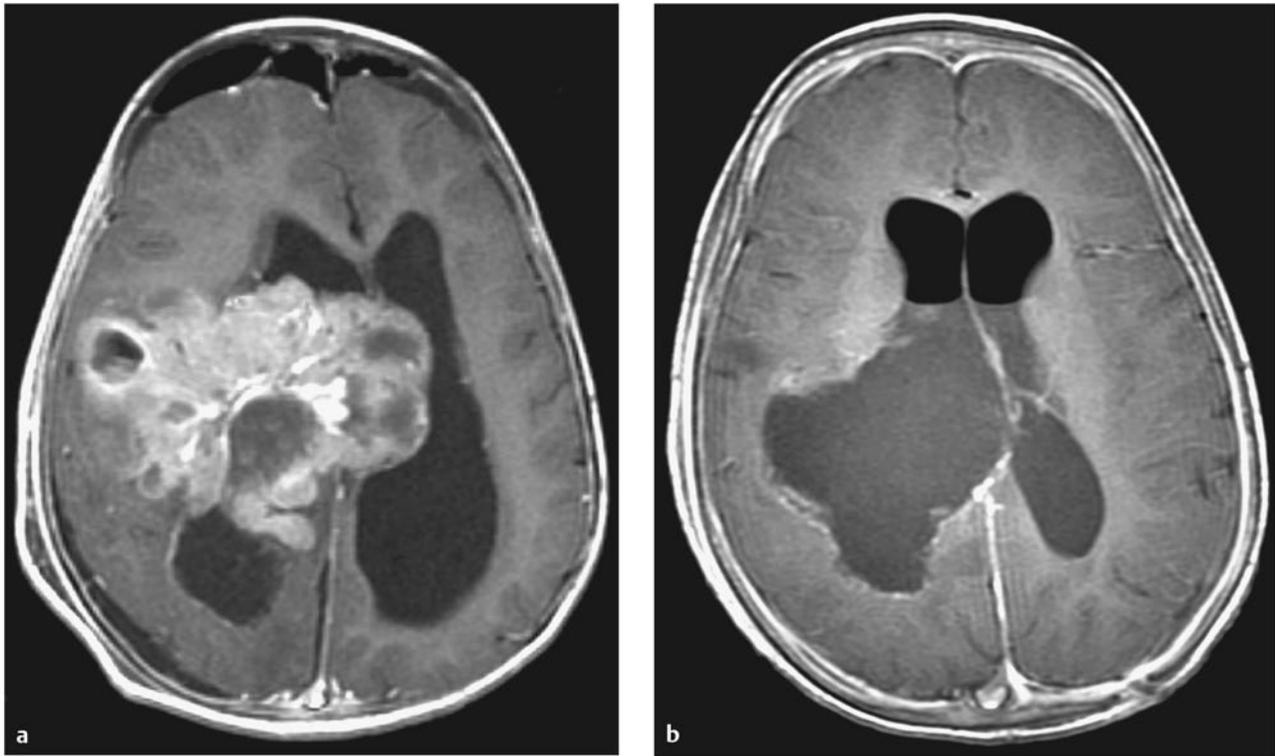


Fig. 33.8 Ependymoma. (a) Preoperative and (b) postoperative axial magnetic resonance images following contrast administration in a 14-month-old boy with a supratentorial ependymoma. The tumor occupies a significant portion of the right cerebral hemisphere. The child underwent total excision of an anaplastic ependymoma at second-look surgery following adjunctive preoperative chemotherapy.

treated for ependymoma was a 3-year PFS rate of approximately 26% as assessed by the CCG.⁴³ Although whether pathology is predictive of outcome is controversial, the CCG study enrolled only patients with a malignant or anaplastic histology. The POG evaluated 48 children younger than 3 years with ependymoma (classic and anaplastic varieties) and found a radiologic response rate of 48% with a treatment approach that used neoadjuvant chemotherapy with the intent of delaying or completely avoiding radiation therapy. The extent of resection was found to be the most important predictor of outcome, with 5-year OS rates of 66% and 25% for those children undergoing gross total excision and subtotal excision, respectively. The study also established that the disease control rates, which are similar shortly after therapy, diverge with longer follow-up between patients younger than 1 year and those between 2 and 3 years of age at the time of treatment. Thus, at 5 years, the younger patients had a 26% survival rate, whereas the older children had a survival rate of 63%. The conclusion drawn from these important observations was that a delay of radiation of more than 1 year adversely affects survival.

As is true in children of all ages, the principal site of recurrence is usually at the primary site of disease, with a minority of children having disseminated disease at the time of progression. The pattern of recurrence and poor control rates have led to the use of highly conformal radiation therapy as a therapeutic adjunct. This approach has been used in 88 patients whose mean age was 2.85 years, with 15 patients younger than 18 months at the time of treatment, at St. Jude Children's Research

Hospital in Memphis, Tennessee.⁷³ With a median follow-up of over 38 months, the 3-year PFS rate was 75%. In interpreting these data, it is important to bear in mind that 84% of the patients had confirmed gross total excision of their tumor before irradiation.

Because of the wide recognition that the extent of surgical excision positively affects outcome, other strategies, including surgical re-exploration (so-called second-look surgery), have been advocated for residual ependymoma. This approach has been used in small, single-institution series with initial success toward achieving gross total excision.^{74,75}

33.9 Astrocytoma

A detailed account of astrocytomas in children can be found in Chapters 42 and 43. However, several characteristic features of astrocytomas in very young children warrant separate consideration.

33.9.1 Optic Pathway Gliomas (Chiasmatic/Hypothalamic Gliomas)

Gliomas of the optic pathway (chiasmatic/hypothalamic gliomas) account for nearly 20% of all intracranial tumors in children younger than 2 years.⁷⁶ These children can present with several manifestations. Alterations in vision usually manifest as nystagmus, spasmus nutans, or poor fixation. Raised

intracranial pressure from noncommunicating hydrocephalus is most frequently identified by progressive macrocrania. The diencephalic syndrome of emaciation, or Russell syndrome, is quite specific for a hypothalamic glioma during infancy; it is characterized by failure to thrive, normal axial growth, and increased growth hormone levels.⁷⁷ The most frequent manifestations of alterations in endocrine function are precocious puberty and growth hormone deficiency. Although neurofibromatosis type 1 (NF1) is present in roughly half of all children with chiasmatic/hypothalamic glioma, most children younger than 2 years in whom this tumor is diagnosed do not have NF1.⁷⁸ Although the less frequent association with NF1 may in part be responsible for the poorer prognosis of children younger than 2 years of age, the tumor may have a more aggressive biological behavior in very young children, and there is a reluctance to utilize radiation therapy. The current treatment strategy includes chemotherapy only in the presence of symptom progression or radiographic changes. With such an approach, the 5-year PFS rate for children younger than 3 years of age at diagnosis has been reported at 63%.⁷⁸

33.9.2 Pilocytic Astrocytoma

A recently described variant of hypothalamic/optic pathway pilocytic astrocytoma, pilomyxoid astrocytoma has been recognized to have a predilection for younger children; the mean age at onset is 18 months.^{79–81} This subtype of pilocytic astrocytoma is identified on the basis of the histologic phenotype, but the diagnosis carries a different set of clinical features. In addition to causing symptom onset at a younger age, these tumors exhibit a more aggressive behavior, a higher rate of local recurrence, a substantial rate of CSF dissemination, and a shorter PFS (mean, 26 months) and OS (mean, 63 months).⁷⁹ The histologic identification is based on a monomorphous rather than a biphasic pattern of cells on a myxoid background. The tumor is notably absent in Rosenthal fibers and has rare eosinophilic granular bodies, features quite commonly found in the pilocytic counterpart. The recognition that pilomyxoid astrocytoma occurs predominantly in the infant age group may partly explain the well-known association between poor prognosis and young age in children with hypothalamic/optic pathway astrocytomas. At the current time, the treatment of pilomyxoid astrocytoma is analogous to that of pilocytic astrocytoma, but with better classification of this subtype, the therapeutic approach may change.

33.9.3 Supratentorial High-Grade Astrocytoma

The malignant astrocytomas (WHO grades III and IV) that occur in young children, although much less frequent, appear to be unique compared with similar histologic tumors in older children and adults. The overall outcome in children with malignant astrocytoma is more favorable in most series. However, infants with malignant astrocytoma do not possess the same prognostic advantage realized in older children. Infants with malignant astrocytoma present a treatment dilemma, not unlike infants with other supratentorial malignant tumors, owing to the large size and hemorrhagic potential of the tumor and to treatment limitations caused by adverse events related to

therapy. The CCG experience concerning the outcome of 39 children younger than 24 months of age treated with neoadjuvant chemotherapy indicated an overall response rate of 24%.⁴³ The most significant variable affecting outcome was tumor pathology, with 3-year EFS rates of 44% and 0% for anaplastic astrocytomas and glioblastomas, respectively.

Some molecular analytic data indicate that malignant astrocytomas in infants are biologically distinct. Mutations in the tumor suppressor gene *TP53* appear to be distinctly less frequent in tumors from children younger than 3 years of age than in those from older children and adults.⁸² Given that overexpression of p53 has been correlated with an unfavorable prognosis for children with malignant gliomas, this reduced incidence of mutagenesis may indicate a better response rate to particular therapies.⁸³

33.10 Choroid Plexus Tumors

Choroid plexus tumors are truly unique tumors of very young children, with the majority of patients younger than 3 years of age at the time of diagnosis.⁸⁴ Choroid plexus tumors account for approximately 0.5% of all intracranial tumors but nearly 12% of all brain tumors in children younger than 2 years of age. Hydrocephalus invariably exists in children with choroid plexus tumors. The mechanism is probably multifactorial, but this entity represents the only known common cause of CSF overproduction resulting in hydrocephalus (► Fig. 33.9). After complete tumor removal, treatment of hydrocephalus may still be needed, given the likely association with intraventricular hemorrhage or inflammatory reactions resulting from surgery and mechanical distortion of the intraventricular CSF pathways. The rate of resulting need for CSF diversion by way of shunting has been reported to be as high as 75%.⁸⁵ Subdural effusions tend to require further management nearly as frequently as hydrocephalus. The large size of the tumor, degree of ventriculomegaly, and extended duration of the surgical cases all probably contribute toward this postoperative management issue. Closure of the corticectomy site with fibrin sealant following tumor removal has shown some success in isolating the intraventricular compartment from the subarachnoid space.

These tumors are some of the most surgically challenging lesions in infants owing to their large size, invasiveness, and hypervascular nature, with intraoperative mortality not infrequently reported resulting from blood loss.⁸⁷ The surgical approach needs to be tailored such that the vascular pedicle or tributaries are identified early and controlled before the tumor is removed. Depending on the site within the lateral ventricle, a high parietal approach offers early recognition of the medial posterior choroidal vessels, whereas an inferior temporal approach offers early control of arterial feeders from the anterior choroidal artery through the choroidal fissure in the temporal horn of the lateral ventricle. Some attempts to reduce tumor vascularity preoperatively with endovascular embolization have been reported.^{86–89} These attempts have historically been limited, given the technical challenges associated particularly with cannulating the medial posterior choroidal vessels; however, when possible, the benefits are apparent and may contribute toward a simpler resection. One recent report even suggests

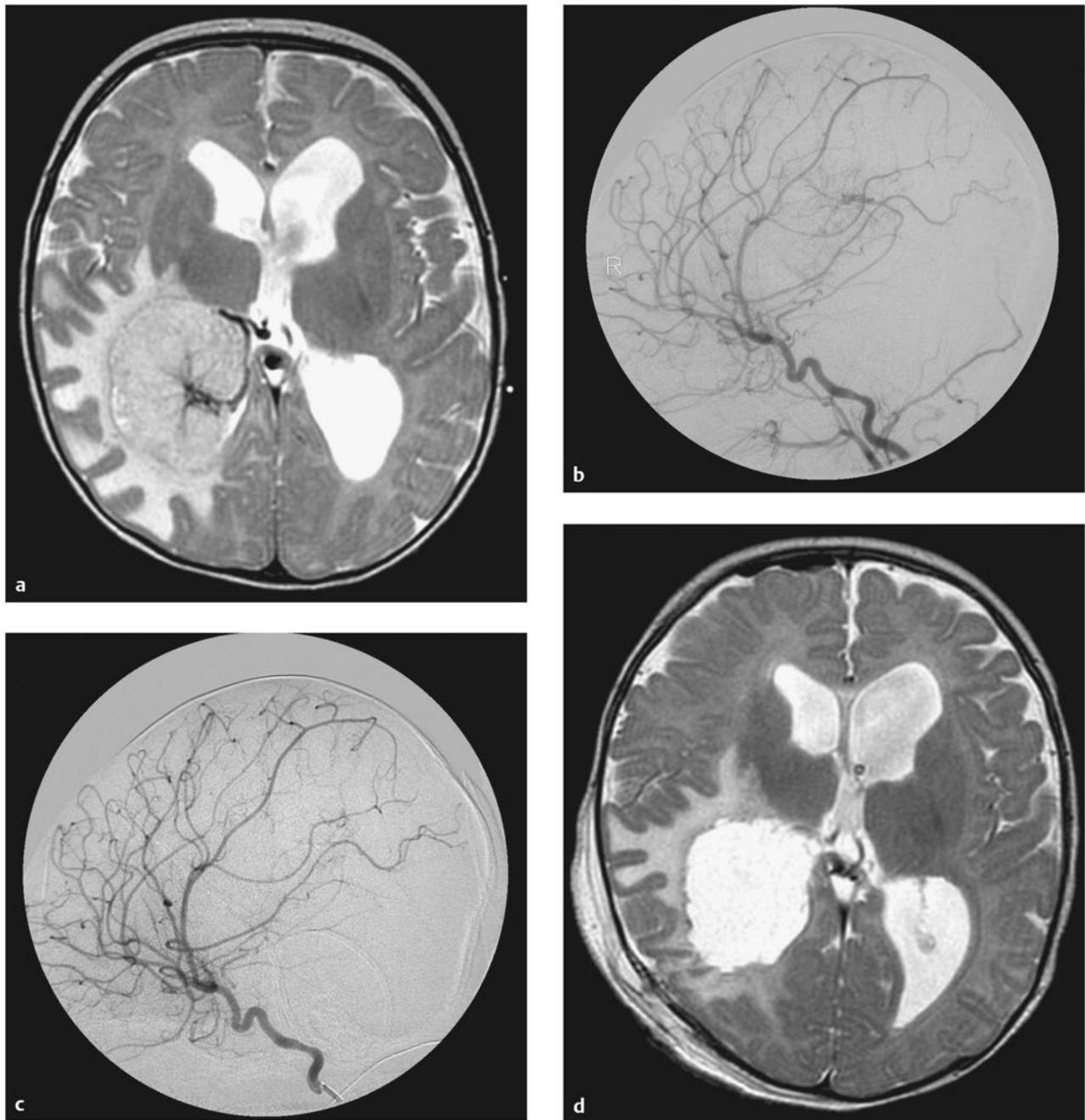


Fig. 33.9 Choroid plexus papilloma. Representative magnetic resonance images from a 4-month-old boy who was evaluated for increasing head circumference. (a) An axial T2-weighted image revealed a large left intraventricular mass and ventriculomegaly. Given the expected tumor vascularity, (b) an angiogram was obtained that confirmed the presence of a very rich arterial supply. The lateral projection of the right internal carotid artery depicts the tumor blush principally from the right anterior choroidal artery. (c) The postembolization angiogram demonstrates a reduction in vascular blush. (d) The postoperative axial T2-weighted image confirms that a gross total excision of the tumor was accomplished.

complete remission of a presumed choroid plexus papilloma by embolization alone at 16-month follow-up.⁹⁰ An example of such an approach is shown in ► Fig. 33.9.

Choroid plexus papilloma (WHO grade I) occurs about twice as often as choroid plexus carcinoma.⁸⁷ The differentiation of these tumors is based on careful interpretation of the pathologic specimen (► Fig. 33.10). Contrary to the predominantly fourth ventricular location seen in adults, the lateral ventricle is

the most common location for choroid plexus papilloma in children. These tumors are treated with primary resection, which in contemporary series is achieved in as many as 96% of cases.⁸⁷ With complete excision, the 5-year survival rate has been reported to be as high as 100%. The atypical choroid plexus papilloma (WHO grade II) is an entity of intermediate malignancy and prognosis relative to papilloma and carcinoma of the choroid plexus.⁹¹

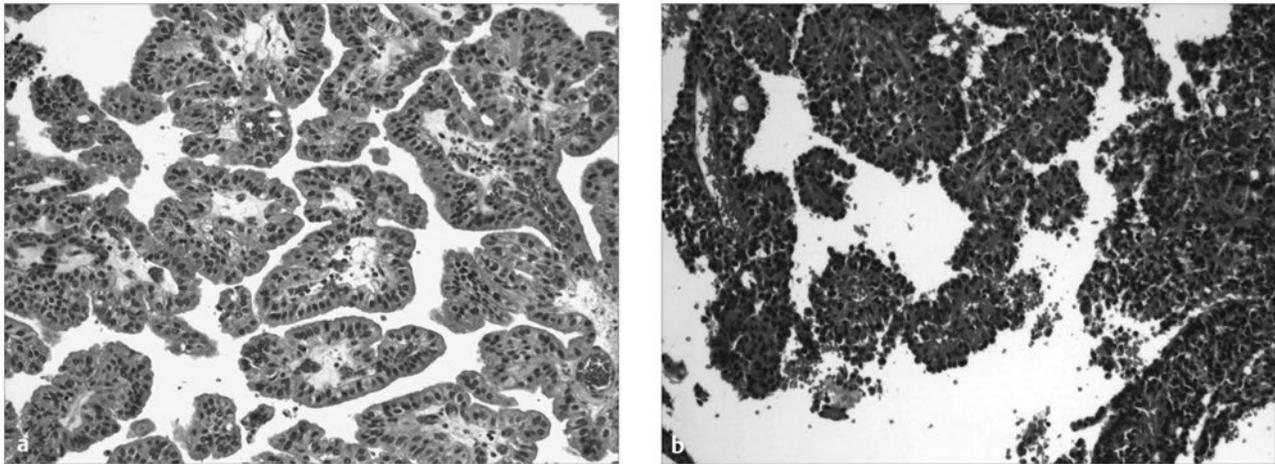


Fig. 33.10 Choroid plexus tumors. Histologic samples from (a) a choroid plexus papilloma and (b) a choroid plexus carcinoma. Both recapitulate a papillary cytoarchitecture, but the carcinoma shows foci of solid growth and prominent cytologic atypia.

Choroid plexus carcinoma (WHO grade III) is a rare disease, accounting for 1 to 4% of all brain tumors in children. This tumor differs from its more common counterpart, choroid plexus papilloma, in that it most frequently arises within the lateral ventricle, presents during infancy, is frequently invasive, and has a relatively poor prognosis. The 5-year OS rate ranges from 40 to 50%.^{92,93} Treatment modalities have ranged from surgery alone to surgery with postoperative radiation therapy and chemotherapy. Most reports suggest that the prognosis is improved with complete surgical resection^{87,92–95} and the use of adjuvant chemotherapy.^{87,93–100} Although no consensus exists about the value of chemotherapy after total excision, published response rates with measurable disease certainly indicate that there may be a benefit in this context. Complete surgical resection is hampered by the typically large size and vascularity of these tumors in young children with a proportionally small circulating blood volume. In one contemporary study, the rate of surgically related mortality due to complications of excessive hemorrhage was as high as 30%.⁸⁷ Irradiation, whose role is supported by some previous evidence, has fallen out of favor, given the typically young age of afflicted children and the known detrimental sequelae of irradiation during infancy.

Loss of function of *TP53*, implicated in a variety of tumors, as previously mentioned, and responsible for the Li-Fraumeni syndrome, has recently been shown to be associated with higher grades and poorer outcomes in the approximately 50% of sporadic and syndromic choroid plexus tumors in which it is found, compared with the intriguingly large fraction of these tumors that exhibit other alterations in this gene.¹⁰¹ While mechanistic studies are ongoing, screening for Li-Fraumeni syndrome and molecular analysis of somatic tumor tissue may play an important prognostic role in the future treatment of this disease.^{102,103}

33.11 Atypical Teratoid/Rhabdoid Tumor

Since the earliest description of atypical teratoid/rhabdoid tumor (AT/RT) as a separate entity, better clinical descriptions

have become available, and the tumor has undergone molecular characterization as well.³⁶ AT/RT frequently occurs in children younger than 2 years of age; the mean age at diagnosis is 17 months.^{36,104,105} The tumor has a predilection for the posterior fossa and pineal region; however, it also occurs with some frequency in the supratentorial compartment. In fact, the tumor occurs about twice as frequently in the infratentorial compartment as in the supratentorial location. Surgical resection is challenging owing to the hypervascular nature of this tumor, and the difficulty is compounded by the young age and relatively small circulating blood volume of the patients.

The histologic appearance reflects the malignant nature of the tumor, evidenced by a compact and highly cellular lesion with widely pleomorphic features, mitotic figures, and areas of necrosis. The small, compact cytoarchitecture is reminiscent of medulloblastoma, and it is likely that many of these tumors are incorrectly diagnosed as such³⁶ (► Fig. 33.11). A population of large, pale cells with “rhabdoid” features is responsible for the current nomenclature. The embryonic nature of the tumor is confirmed by its immunophenotypic diversity, which indicates mesenchymal and epithelial differentiation (vimentin, glial fibrillary acidic protein, epithelial membrane antigen, cytokeratins, synaptophysin, chromogranin, and smooth muscle actin).¹⁰⁶ Chromosomal and genetic analysis confirms that this tumor differs from other highly malignant embryonal tumors. Cytogenetic analysis yields the frequent loss of chromosome 22, with involvement of the chromatin-remodeling tumor suppressor gene *INI1/hSNF5* detectable in a majority of cases.^{107–111}

With multimodal therapy, the mean postoperative survival is between 6 and 11 months, usually marked by early recurrence and CSF dissemination.^{104,112} Lasting responses to multimodality therapy have been reported.^{113–117} Of the long-term survivors, most have been treated with aggressive surgical resection, radiation therapy, and chemotherapy. The chemotherapy regimen in those cases was based on a multiple-agent regimen designed by the Intergroup Rhabdomyosarcoma Study III (IRS III) for parameningeal rhabdomyosarcoma. Notably, this approach incorporates the use of both systemic and intrathecal chemotherapy. Survivors treated with this approach are reported to

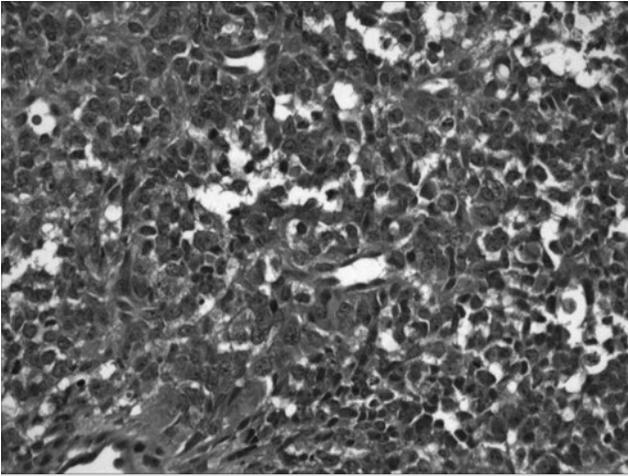


Fig. 33.11 AT/RT. Low-power hematoxylin and eosin (H&E) stain of an atypical teratoid/rhabdoid tumor. Large cells contain moderate amounts of pink cytoplasm, hyperchromatic nuclei, and prominent nucleoli. The compact nature of the tumor with a notable frequency of mitotic figures is reminiscent of a medulloblastoma. Note the large vacuoles, which produce a “starry sky” pattern.

have a mean disease-free interval of just over 3 years, with one pilot study achieving a median OS of 50 months.^{113,117}

33.12 Teratoma

Teratoma is the most common primary brain tumor diagnosed at the time of birth.¹¹⁸ There is little debate that this tumor is truly a congenital neoplasm, given the very early age at presentation, the occurrence of prenatal diagnosis, and the frequent association with stillbirth. An enlarging head circumference resulting from a massive intracranial mass is the typical presentation in children born alive. In fact, the accelerated growth characteristics have led to several reports of extension of the tumor beyond the confines of the cranial compartment.^{119,120} The histologic hallmark of this tumor is the recognition of derivatives from all three primordial germ layers (endoderm, mesoderm, and ectoderm). The tumors can be graded as benign or malignant, the latter defined by poor differentiation. The overall outcome for children with a teratoma is poor, usually because the massive size and extensive growth characteristics of the tumor make surgical removal impractical. The exception to this poor outcome is the situation in which a benign teratoma can be totally excised, in which case long-term survival is expected.

33.13 Desmoplastic Tumors of Infancy

Several tumors of infancy exist that share very similar anatomical, histologic, and biological features. These rare tumors account for approximately 1% of all tumors in infants.¹²¹ Macroscopically, they are found exclusively in the supratentorial compartment and are located superficially at the cortical surface. They variably attach to the dura, possess multiple circumferential cysts, and attain voluminous sizes (► Fig. 33.12).^{122–124} Their superficial location is manifested in a growth pattern that can

cast the gyral and sulcal patterns, creating an almost multilobular pattern.

These tumors share not only gross morphologic features but also microscopic elements (► Fig. 33.13). The most prominent characteristic is the microscopic finding of a robust desmoplastic stroma. This background of a dense fibrous connective tissue rich in reticulin fibers is reminiscent of mesenchymal tumors. Frequent mitotic figures and spindle cells that resemble those of sarcomatous tumors frequently lead to an inaccurate diagnosis and an incorrect ominous prognosis.¹²³ The tumors are generally categorized as desmoplastic infantile ganglioglioma or desmoplastic cerebral astrocytoma of infancy, depending on whether the predominant immunohistochemical pattern of staining is astrocytic or ganglionic, respectively. Owing to the somewhat unclear classification of these tumors, desmoplastic infantile ganglioglioma has been referred to as a gliofibroma, whereas desmoplastic cerebral astrocytoma of infancy has been classified as a superficial cerebral astrocytoma. Because of this varied terminology but similar clinical and histologic features, attempts have been made to aggregate these tumors into the single clinicopathologic entity of desmoplastic supratentorial neuroepithelial tumors of infancy.^{125,126}

Regardless of the nosology or descriptive histology, the biological behavior of these tumors appears to be analogous. With rare exception, they have a very indolent behavior, meaning that total surgical excision is expected to render a cure. Long-term disease-free intervals are the norm after surgical removal. The extreme sizes and cortical location of these tumors occasionally lead to incomplete surgical resection. Residual tumor can remain static without interval growth for extended periods or even involute, with a radiologically defined reduction in tumor size.¹²² This latter point emphasizes the usual lack of need for adjuvant therapy after surgery, even in the case of an incompletely removed tumor. Because chemotherapy has been reported to result in an objective tumor response, some recommend chemotherapy when total surgical excision is not possible.¹²³ These recommendations were based on a small number of patients culled from a cooperative study; their diagnosis was incorrect, and they were thus treated with therapeutic regimens intended for patients with high-grade glial tumors. The indolent behavior of the tumors and their occasional spontaneous involution without therapy suggest that it would be conjectural to infer a causal relationship between chemotherapy and tumor response in desmoplastic tumors of infancy.

33.14 Treatment

33.14.1 General Considerations

Therapeutic strategies are tailored to individual cases based on tumor location, size, histology, and the patient's clinical condition. Thus, the optimal form of treatment for infants with primary brain tumors varies substantially. The treatment of young children with malignant brain tumors is significantly more challenging than the treatment of older children or adults because of the well-recognized detrimental effects of therapeutic intervention on the developing CNS. As a result, the overall outcome for infants and young children is appreciably worse than it is for their older counterparts. The prognosis depends mainly on tumor type, but generalizations about outcome have been

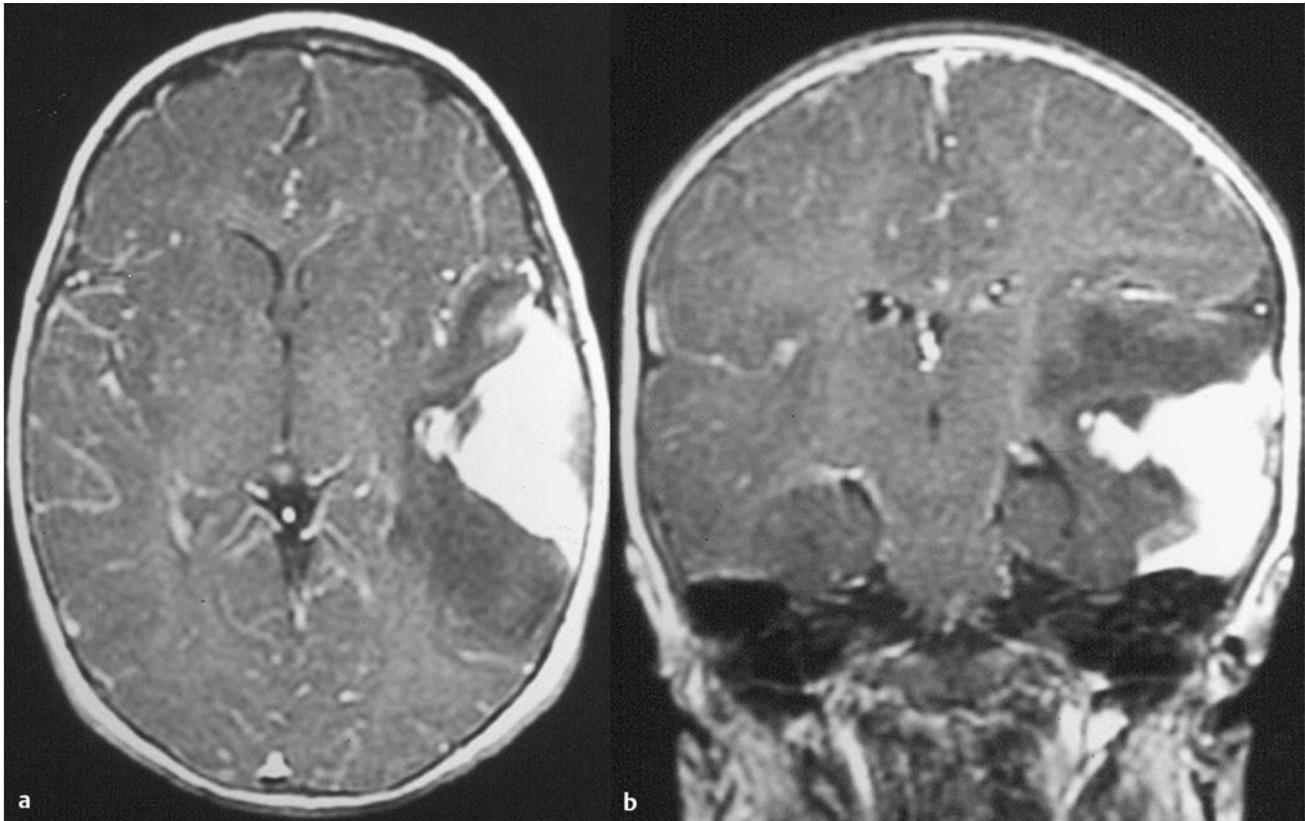


Fig. 33.12 Desmoplastic infantile ganglioglioma. (a) Axial and (b) coronal magnetic resonance images of a 5-month-old boy who presented with seizures. A supratentorial location, superficial or cortical origin, and very large size are all characteristic features manifested in this desmoplastic infantile ganglioglioma.

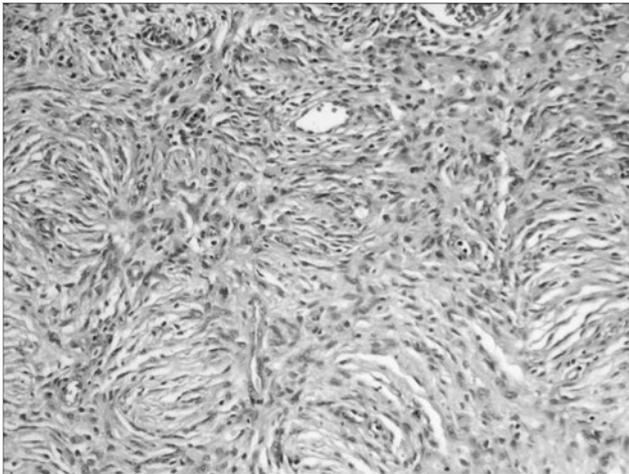


Fig. 33.13 Desmoplastic infantile ganglioglioma. Strands of collagen interspersed with neuroglial cells showing eccentric pink cytoplasm in a desmoplastic infantile ganglioglioma. The stromal pattern is reminiscent of a mesenchymal sarcoma.

recognized for decades based on studies and databases that include all histologic subtypes. The Surveillance, Epidemiology, and End Results (SEER) Program indicated that in children younger than 2 years who were treated for benign and malignant tumors, the 5-year survival rate ranged from 23 to

36%.^{127,128} This dismal outcome has been attributed to a variety of causes, including less aggressive surgical resection, more aggressive biological behavior, greater metastatic potential, and intentional avoidance of radiation therapy. Several features have been implicated in the worse outcome of very young children treated for a brain tumor. Primary among these probable causes are the inability to achieve a total tumor resection because of very large tumor dimensions, relatively large blood loss, and a more infiltrative growth pattern. It has been suggested that staged surgical procedures and second-look surgery after chemotherapy offer an advantage over the aggressive surgical removal of brain tumors.

Additionally, the relatively poor prognosis for children younger than 2 years with malignant brain tumors results from the avoidance of conventional irradiation. Over the past two to three decades, the detrimental effects of therapeutic doses of irradiation on neurodevelopmental outcome have justifiably led toward the development of therapeutic protocols that integrate neoadjuvant chemotherapy with the intent to postpone or eliminate radiation therapy.^{43,52,129} High-dose chemotherapy with autologous stem cell transplantation has been reported to positively influence outcome in particular diseases. Another therapeutic design intended to replace craniospinal irradiation incorporates intrathecal chemotherapy.

Some recent concepts mandate a more detailed discussion with respect to the treatment of infants with newly diagnosed

primary brain tumors. These evolving strategies, although not universal, are based on early cooperative group trials, but most commonly on pilot study data from single-institution investigations. All of these approaches share a conceptual framework of maximizing the disease-free interval while minimizing the early or late effects of therapy.

33.14.2 Surgical Treatment

With few exceptions, the extent of surgical resection is positively correlated with overall outcome. The surgical management of young children with brain tumors significantly differs from the surgical management of older children and adults. Unequivocally, the operative mortality rate exceeds that for older children undergoing craniotomy for primary brain tumors. In contemporary series, the mortality rate has ranged from 7.3 to 33% for children younger than 2 years at the time of surgery.^{14,17,20,29} Mortality rates from surgical intervention are most commonly attributed to blood loss, and it is thus intuitive that tumor histology influences the outcome of infants undergoing craniotomy for tumor removal. This point has been elaborated on in a review of 76 children younger than 2 years, whose surgical mortality rate ranged from 0% for benign tumors to 20% for highly malignant tumors.¹⁹ However, with the use of advanced perioperative adjuncts, including preoperative magnetic resonance (MR) imaging, microneurosurgical techniques, pediatric neuroanesthesia, and pediatric intensive care unit monitoring, a 0% surgical mortality rate can be achieved.²⁷ This result is highly commendable, given that malignant tumors accounted for 50% of tumors and that total excision was accomplished in 55% of the 22 patients in that particular series. Clearly, mortality rates from surgery can be influenced by the definition used of a surgically related death and the period of time during which death is attributed to the surgical procedure. What is certain is that surgical morbidity and mortality are not insignificant, and that the operative management of these children should not be undertaken without a dedicated and multidisciplinary approach toward the treatment of infants with brain tumors.

Many features demand that standard procedures be tailored to ensure the safety of infants undergoing a craniotomy for brain tumor removal. First, the child's small size has a direct impact on temperature control and circulating blood volume. The problem of a small circulating blood volume is exacerbated by the voluminous size and hemorrhagic nature of many infantile tumors. Second, the lack of skeletal maturity introduces a risk for skull fracture and intracranial injury with standard skull fixation. Third, the immature neuronal circuitry and young developmental age limit the ability to perform intraoperative or preoperative cortical mapping. These points are elaborated upon in the following discussion, with recommendations offered for optimizing each goal while maintaining safety.

The relatively high ratio of body surface area to body weight in infants creates a situation in which convection rapidly lowers the body temperature. This circumstance is magnified by the slowed metabolic rate of the anesthetized child, the lack of an integumentary barrier within the surgical field, the infusion of intravenous fluids, the paucity of stores of yellow fat, and the cooling induced by standard preparatory scrubs. The relatively large head size of the young child also affects the ability to

maintain normothermia during intracranial procedures. Many of these issues are minimized by employing a rational and preventive approach. To reduce convective cooling, the ambient room temperature should be elevated. Thus, most neonatal surgery should take place only in operating rooms in which independent temperature control is available. A simple maneuver to help minimize temperature loss during the surgical scrub is to prewarm the preparatory solutions in the surgical incubator before use. In addition to reducing the amount of heat loss, warm air currents or convective warming blankets can be used to warm the child. Warming systems need to be used with care so as to avoid having any heating elements in direct contact with the skin. The replacement of circulating blood volume with either intravenous fluids or blood replacement products is frequent in young children undergoing resection of primary brain tumors, and all transfused fluids should be warmed before administration to help maintain physiologic body temperature.

Meticulous hemostasis, although a mandatory component of surgery, especially in infants, is not in itself a guarantee against potential poor outcomes. Thus, preparations need to be coordinated before the initiation of the surgical procedure. Intravenous access that can accommodate rapid transfusion is essential, as is continuous blood pressure monitoring with an arterial line. Appropriately cross-matched whole blood should be available in the surgical suite at the initiation of the procedure. The judicious use of bipolar cautery, hemostatic clips, and bone wax is critical. Although the hemorrhagic nature of the tumor is beyond control, the technique of tumor removal will have a bearing on the degree of blood loss. For instance, thorough coagulation of the tumor surface before debulking can reduce blood loss. Achieving control of the tumoral region receiving the dominant blood supply is also useful. The latter point is exemplified in the removal of choroid plexus tumors from an intraventricular location. Selecting an approach that affords visualization and early control of the choroidal vasculature is recommended. Although the surgical technique can clearly reduce the degree of blood loss, the nature of certain tumors makes their safe removal almost prohibitive in infants. This scenario is most notable in children with highly malignant neoplasms, such as choroid plexus tumors and AT/RTs. The circulating blood volume of neonates is estimated to be 90 mL/kg (or some 300 mL in the average child born in the developed world), that of infants 85 mL/kg (some 1 L in the average 2-year-old), and that of older children approximately 80 mL/kg.^{130,131} This awareness of total circulating blood volume can help in making decisions about staging the procedure and when to consider supplementing platelets and plasma. Although laboratory measurements of platelets and coagulation profiles can guide such decisions, blood loss equivalent to one circulating blood volume is a reliable indicator that these products should also be administered.

The fragility of the infant skull, owing to its thinness and the presence of cranial sutures, create a potentially dangerous situation for the use of rigid pin fixation, with risks including scalp laceration, calvarial fracture, and epidural hematoma.¹³² This obstacle is avoided by using nonrigid methods of fixation, such as a cushioned horseshoe head frame. However, the lack of rigid fixation diminishes or abrogates the effectiveness of surgical adjuncts such as rigid self-retaining retractors and frameless stereotaxy. Furthermore, with prolonged procedures, the additional concern of pressure necrosis of the scalp necessitates

intermittent intraoperative repositioning. The risk of pin fixation is somewhat lessened by using an increased number of pins in an effort to distribute the pressure more evenly and decrease torsional strains on the skull. Specially designed pins are available that have a reduced length and a collar to reduce the risk for transcranial migration. Depending on the expected duration of the surgery, the maturation of the child, and the expected need for intraoperative adjuncts, the decision to use pin fixation needs to be tailored. There is no general consensus on the safe use of pin fixation in young children, but a common recommendation is to avoid pin fixation in children younger than 2 years.¹³³ In very young children, the risk for cranial perforation and cranial compression is lessened somewhat by utilizing head frames that accommodate more than three pins so as to disperse pressure.

Recent attention has focused on stereotaxy adjuncts that do not rely on rigid fixation, with reports of successful navigation utilizing frameless, pinless approaches to secure a reference frame to the skull. These approaches have included the application of an affixed or adhered reference for electromagnetically based tracking and the use of beanbag-based supportive pseudofixation.¹³⁴⁻¹³⁶ Additionally, modifications have been developed for frame-based stereotactic devices, thus enabling their use for less involved procedures, such as stereotactic biopsy.¹³⁷ Practically, given that the great majority of tumors in this age group attain very large dimensions and are associated with significant hydrocephalus and/or tumor cysts, the reliability of stereotaxy based on preoperative imaging is quickly diminished intraoperatively.

Intraoperative adjuncts, including cortical mapping and stereotactic guidance, have limited use in very young children. Infants' inability to cooperate and their immature developmental status imply that cortical mapping cannot reliably or practically be used. Furthermore, extraoperative mapping by way of functional MR (fMR) imaging or intraoperative mapping with cortical bipolar stimulation is difficult and typically yields unreliable information. Some attempts at using fMR imaging in sedated children have resulted in a paradigm that works with passive stimulation techniques.¹³⁸ Most children do not exhibit cerebral dominance until at least 2 to 3 years of age; therefore, this limitation may not be as problematic as it is in older children or adults, given the known potential for cerebral plasticity during infancy.

Alternatively, transfontanel or transcortical ultrasonography can be used intraoperatively, depending upon the intended goal of navigational assistance. For navigational or directional assistance, transfontanel ultrasonography can be useful. This modality also serves as an important adjunct in infants undergoing volumetric tumor resections, and it has the added appeal of not requiring pin fixation.¹³⁹ Intraoperative MR imaging has advantages over these modalities in that no head fixation is required, large volume shifts can be easily accounted for with serial imaging, and the spatial resolution approaches that obtained with extraoperative diagnostic imaging.¹⁴⁰

Closure of the craniotomy defect in the very young child must take into account the continuance of the rapid phase of cranial vault expansion through infancy. Craniotomy flap repair must both ensure cerebral protection and avoid deformity; resorb-

able plating systems that offer secure bony reconstruction while providing plasticity (and avoiding the phenomenon of intracranial "displacement" of metallic hardware during the process of outward calvarial remodeling) have become the preferred mode toward these ends. Commercially available resorbable plating systems utilizing polyesters of lactic acid (polylactic acid, or PLA) and glycolic acid (polyglycolic acid, or PGA) have been widely studied in the craniofacial literature. PLA derivatives have intrinsic strength and durability related to their hydrophobic and crystalline properties, but these qualities may also make them more likely to cause foreign body reactions. PGA polyesters are more absorbable, but they have less tensile strength. Modern plating systems are copolymers and afford the benefits of both.¹⁴¹⁻¹⁴⁵

33.14.3 Adjuvant Therapy

The conventional approach of postoperative radiation therapy with or without chemotherapy in the treatment of malignant primary brain tumors in infants and very young children has been unsatisfactory.^{52,146,147} The use of cranial irradiation in children younger than 3 years is associated with an unacceptable rate of adverse late effects, including growth failure, mental retardation, leukoencephalopathy, and secondary cancers.^{61,148-157} Thus, various therapeutic strategies have been explored in an effort not only to increase survival rates but also, just as importantly, to improve the quality of life of survivors. Some of these therapeutic approaches are outlined below.

Neoadjuvant Chemotherapy

The unacceptably high incidence of adverse sequelae in young children after conventional craniospinal radiation therapy has been the primary impetus for the development of alternative therapeutic strategies. One such approach has employed the concept of postoperative chemotherapy with the intent to either eliminate or delay the use of irradiation. At MD Anderson Cancer Center, children younger than 36 months who had brain tumors received chemotherapy without radiation therapy, with a 5-year PFS rate of 55% for children with medulloblastoma.¹⁵⁸ The POG in 1993 reported on the results of a larger cooperative study in which postoperative chemotherapy was used with the intent of delaying radiation therapy for 1 to 2 years following surgery.⁵² In that study of nearly 200 children younger than 3 years at the time of study entry, the PFS rate was 41% at 1 year for children ages 24 to 36 months and 39% at 2 years for those younger than 24 months at diagnosis. Embryonal tumors indicated a poorer outcome, whereas complete surgical removal was a positive predictive feature. Most recurrences were observed early at the primary site. Similarly, the CCG reported on their results with an approach in which neoadjuvant chemotherapy and delayed involved field or craniospinal radiation therapy were used in children younger than 18 months at diagnosis.⁴³ That group reported 3-year PFS rates of 22% and 26% for children with medulloblastoma and ependymoma, respectively. Overall, that rate was significantly dependent on the presence or absence of metastatic disease (11% compared with 29%).

A primary chemotherapy approach has been used in an attempt to avoid cranial irradiation and many of the adverse neuroendocrine and neurodevelopmental sequelae that are nearly ubiquitous with radiation therapy in infancy.⁵¹ Pre-irradiation chemotherapy results in a higher radiographic response rate in children younger than 36 months than in older children (33% vs. 11%).¹⁵⁹ In summary, improvements in objective response rates and disease-free intervals, although not lasting, are accomplished with some regularity with the use of neoadjuvant chemotherapy before irradiation in very young children. Furthermore, the detrimental sequelae of immediate postoperative radiation therapy do appear to be attenuated with such an approach.

However, it has been found on longer follow-up analysis that disease recurrence is somewhat influenced by the duration of chemotherapy. Infants treated with chemotherapy for longer than 12 months were found to have a greater likelihood of experiencing disease recurrence than were children receiving 12 months or less of chemotherapy followed by irradiation.^{12,160} This divergence in outcome is attributed to a longer delay in offering radiation therapy.

Some evidence indicates that although the treatment design of delayed radiation therapy and neoadjuvant chemotherapy in infants may reduce radiation-induced neurotoxicity, this reduction may be at the expense of second malignancies. In 1997, it was reported that the original cohort of patients treated with the POG protocol had an 11% risk for a second malignancy within 8 years of treatment.¹² This risk was even higher (19%) for children in whom therapy was initiated before the age of 2 years. It was speculated that alkylating agents and topoisomerase inhibitors were the most probable causes, although 2 of 5 patients with secondary malignancies did receive delayed irradiation. The results of such studies are difficult to interpret with respect to causation because an equally likely hypothesis suggests that survivors of childhood cancer probably have a genetic predisposition to oncogenesis.¹⁶¹

Dose-Intensified or High-Dose Chemotherapy

The promising results of using chemotherapy in an effort to delay or avoid radiation therapy in young children, especially as it relates to the reduction of long-term sequelae, has been the basis behind attempts to optimize chemotherapeutic effects on disease control. The intensification of chemotherapeutic regimens has proved to be beneficial in children with various cancers, including neuroblastoma, osteosarcoma, and leukemia. In 1991, a similar approach of dose intensification was undertaken for young children with CNS malignancies (“Head Start”).⁶¹ This approach used intensive neoadjuvant chemotherapy followed by myeloablative chemotherapy and autologous bone marrow rescue in patients who exhibited a radiographic complete response. Radiation therapy was reserved for patients with residual or recurrent disease after therapy. In that particular study, which included patients younger than 72 months of age at the time of treatment, 40% were free of disease progression at a median of greater than 44 months after treatment. Furthermore, neuropsychological examination revealed that cognitive function was preserved in those patients who avoided radiation therapy.¹⁶² This approach has been subsequently used in Head

Start II in patients with disseminated medulloblastoma.¹⁶³ A group of 21 patients with a mean age of 38 months were treated with intensified chemotherapy with autologous stem cell rescue. Patients younger than 6 years of age who had no evidence of disease after chemotherapy did not receive radiation therapy. The 3-year EFS and OS rates were 49% and 60%, respectively. Wide acceptance of this therapeutic approach is somewhat tempered by a toxic mortality rate between 5% and 8%. Whether similarly admirable results are achievable in children younger than 3 years is currently unknown, but the control rates and the improved neuropsychological outcome in children avoiding radiation therapy suggest that this treatment regimen is encouraging for the very young child with a malignant brain tumor.

Preoperative Chemotherapy and Second-Look Surgery

The relatively large tumor size in conjunction with the frequent hypervascularity of many primary brain tumors in infants, as outlined previously, can limit the ability to obtain radical resection safely. For a variety of tumors, a therapeutic strategy of administering preoperative neoadjuvant chemotherapy facilitates aggressive surgical therapy. This approach results in a dual benefit by decreasing the overall size and diminishing the hemorrhagic potential of malignant brain tumors in infants. This therapeutic strategy has been shown to positively influence the treatment of young children with choroid plexus carcinoma^{97,99,100} and PNET.^{97,164}

Benefit has been realized not only with preoperative chemotherapy but also with chemotherapy between treatment regimens. The result is similar in that definitive removal of tumors appears to be enhanced and safer. This approach, termed second-look surgery, has been applied successfully in children with ependymoma, germ cell tumors, and various malignant hypervascular tumors.^{75,165-167} An improved extent of surgical removal been purported, and in addition, second-look surgery has been integrated into treatment protocols before consolidation chemotherapy.¹⁶³ With such an approach, only those children with no evidence of radiographic disease before consolidation chemotherapy had improved outcomes. One recent report of the St. Jude Children’s Research Hospital experience in which neoadjuvant chemotherapy was used before second-look surgery describes radiographic response in 9 of 13 and the achievement of gross total resection in 11 of 13 infants with a variety of pathologies. Two patients required emergency surgery for complications of chemotherapy, including intratumoral hemorrhage and peritumoral edema.¹⁶⁸

Focused Radiation Therapy

Numerous studies have shown a convincing relationship between the use of radiation therapy and the significant late effects experienced by survivors of childhood brain tumors. These untoward effects principally include endocrine abnormalities, impaired axial growth, hearing impairment, neuropsychological dysfunction, and secondary tumors.^{61,148-156} With particular emphasis on the treatment of very young children, an inverse relationship exists between the age at which radiation therapy

is used and the frequency and severity of late effects. Adverse sequelae are found even when low-dose or reduced-dose radiation therapy has been employed.^{157,169} As a result, the liberal use of craniospinal or whole-brain irradiation has been nearly abandoned in treatment approaches for children younger than 3 years. This tenet obviously has had a profound effect upon disease-free intervals in children with many of the primary tumors of infancy, particularly the highly radiosensitive neuroepithelial tumors.

However, recent refinements in focused radiation therapy have brought about a renewal of interest in the potential use of irradiation for very young children. Millimeter scaling in prescribed dosing, reproducible stereotactic localization in children, triplanar imaging with three-dimensional targeting, and inverse dose planning have resulted in the development of highly conformal radiation therapy. This form of radiation therapy is administered through a variety of means, including three-dimensional conformal radiation therapy, stereotactic radiation therapy, intensity-modulated radiation therapy, and proton beam radiation therapy. With the use of conformal fields, the prescribed dose is localized to the tumor, thereby reducing radiation to the surrounding normal brain. Conformal radiation therapy thus offers the possibility of reducing the long-term adverse effects of irradiation and may be applicable in very young children.

Early clinical data indicate that control rates for both benign and malignant tumors of childhood are at least comparable if not better than those achieved with conventional radiation fields.¹⁷⁰⁻¹⁷⁶ With the use of either three-dimensional conformal radiation therapy or intensity-modulated radiation therapy in children with medulloblastoma, limited clinical trials have shown a 65% reduction in exposure of the cochlea to radiation in comparison with exposure when conventional planning was used.^{177,178} This planned reduction in exposure of the cochlea to radiation has been realized in clinical trials of patients with medulloblastoma.¹⁷⁹ These approaches have also shown an 86% local control rate at 10 years in children with medulloblastoma.¹⁸⁰

The application of conformal radiation therapy in infants with intracranial neoplasms has thus far been limited. A report on 88 children with ependymoma treated with three-dimensional conformal radiation therapy at St. Jude Children's Research Hospital has been published.⁷³ The median age of that cohort of patients was 4.5 years, with 15 children younger than 18 months at the time of treatment. The 3-year PFS rate was 75% at a mean follow-up of 38 months. The cumulative local failure rate was 15%, and mean scores on neurocognitive testing were within normal limits at a minimum of 24 months. These encouraging results have led to the integration of conformal radiation therapy as an adjunct for infants in future cooperative group trials.

Although the avoidance of critical normal structures and control rates are achieved with these highly conformal irradiation schemes, concerns about radiation-induced cancer and radiation necrosis have been raised.^{174,178} Altering the energy source through the use of photons is theoretically advantageous with respect to secondary tumors, but longer follow-up will be required before firm conclusions can be drawn about these potential adverse effects.¹⁸¹

Intrathecal Chemotherapy

The prophylaxis and treatment of leptomeningeal dissemination in very young children remain problematic, given the known detrimental effects of craniospinal irradiation in this population of patients. Intrathecal chemotherapy, although logical as a modality of therapy for disseminated or potentially disseminated embryonal tumors, has been limited by technical issues pertaining to therapeutic administration and the limited number of safe intrathecal agents. Because of the widespread use and good safety record of intrathecal methotrexate and cytarabine for children with CNS leukemias or lymphomas, these agents have logically been used most extensively for the treatment of leptomeningeal dissemination of primary brain tumors.

The experience with 62 children with medulloblastoma who were younger than 3 years at the time of treatment was recently reported.⁴² As part of the treatment approach, all children received intrathecal methotrexate as an alternative to craniospinal irradiation. The respective 5-year PFS and OS rates were 82% and 93% for patients who had complete tumor resection, 50% and 56% for patients who had residual tumor, and 33% and 38% for children with macroscopic evidence of disease. Although radiographic leukoencephalopathy was found in nearly half of all patients, no patients exhibited symptoms. Furthermore, a cognitive assessment revealed a reduction in function in comparison with aged-matched controls but better function in comparison with historical controls treated with craniospinal irradiation. It thus appears from this particular study that intrathecal prophylaxis against leptomeningeal disease can be achieved and causes fewer detrimental effects than conventional craniospinal irradiation in very young children.

Encouraging results have also been shown in several patients with highly malignant AT/RTs when an intensive chemotherapeutic approach incorporating intrathecal methotrexate and cytarabine was used.^{113-115,182} The use of intrathecal multiple-agent chemotherapy in most cases was supplemented with focused radiation therapy or craniospinal irradiation. However, given the typical very poor prognosis of children with AT/RT, these results are encouraging and lend further support for adding an intrathecal component to the regimen for leptomeningeal treatment or prophylaxis in young children.

The conceptual issues regarding intrathecal therapy are apparent, and the use of intrathecal methotrexate and cytarabine has further substantiated this approach. Attention has recently been directed to the intrathecal administration of other agents that have proved useful against embryonal brain tumors when administered systemically. Notably, the Pediatric Brain Tumor Consortium has recently investigated in a pilot study the use of intrathecal mafosfamide, a preactivated derivative of the alkylating agent cyclophosphamide, in combination with systemic chemotherapy, conformal radiation, and second-look surgery.¹⁸³ The study established the feasibility of this regimen in 71 children ages 3 years or younger with embryonal tumors; although it appeared to deliver outcomes similar to those in historical controls, this work will likely serve as the basis for future clinical trials specifically designed to evaluate efficacy.

Pearls

- Brain tumors of infancy are commonly composed of histologic subtypes (atypical teratoid rhabdoid tumor, choroid plexus carcinoma, desmoplastic tumors of infancy, pilomyxoid astrocytoma) that are rare in older children and adults.
- Infantile brain tumors are frequently voluminous and located in the supratentorial compartment.
- Surgical mortality in this population is most commonly attributed to blood loss, and appropriate preparations for transfusions are mandatory before surgery is begun.
- Pin fixation should be avoided in infants younger than 2 years in an effort to prevent skull fracture or perforation.
- Second-look surgery after neoadjuvant chemotherapy is an evolving and effective surgical strategy for infants with large malignant tumors.

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34 Supratentorial Hemispheric Gliomas

Ian F. Pollack

The majority of supratentorial hemispheric tumors in children are gliomas,¹ which is similar to the situation in adults. However, a distinguishing feature is the histologic distribution of these tumors; whereas malignant gliomas account for the bulk of intraparenchymal lesions in adults, low-grade gliomas account for the overwhelming majority of such tumors in children. In addition, meningiomas, which are among the most common supratentorial tumors in adults, are rare in children. Another important characteristic of pediatric hemispheric tumors is the strong association between the extent of tumor resection and outcome for virtually all tumor types, including malignant lesions, which may reflect age-related features in the biological behavior of these neoplasms. The present chapter focuses on supratentorial hemispheric gliomas and reviews the epidemiology, pathology and molecular pathogenesis, clinical presentation, diagnostic evaluation, treatment, and outcome of these tumors. In addition, it presents recent advances in intraoperative localization and mapping techniques that have allowed extensive surgical cytoreduction to be achieved with greater safety and reliability.

34.1 Epidemiology

Low-grade gliomas account for almost 60% of supratentorial hemispheric tumors in children and occur at an incidence of approximately 5 cases per 1 million children a year.^{1,2} More than half of such lesions are low-grade astrocytomas. The remainder are mixed gliomas, oligodendrogliomas, gangliogliomas, and a host of less common lesions, such as pleomorphic xanthoastrocytomas,³ dysembryoplastic neuroepithelial tumors,⁴ and desmoplastic infantile gangliogliomas,⁵ which occur most commonly in the pediatric age group. High-grade gliomas comprise approximately 20% of hemispheric lesions.¹

Although a definite environmental or genetic cause for most gliomas is unknown, a subgroup of affected children do have an underlying genetic syndrome, such as type 1 neurofibromatosis (NF1), tuberous sclerosis, or Turcot syndrome, that predisposes them to the development of central nervous system (CNS) tumors. NF1 (discussed in greater detail in Chapter 48) is caused by a mutation in the neurofibromin gene on chromosome 17q11.2,⁶ which encodes a protein with guanosine triphosphatase-activating properties that functions in signal transduction. Although the most characteristic intracranial neoplasms in affected patients are optic pathway gliomas, lesions develop in the cerebral hemispheres in a small percentage of patients. These are generally low-grade gliomas⁷; however, high-grade lesions have also been observed.

Patients with tuberous sclerosis commonly have seizures, mental retardation, and adenoma sebaceum in addition to cortical and subependymal hamartomas (tubers), angioliomyomas of the kidney, rhabdomyomas of the heart, and subependymal giant cell astrocytomas arising in the region of the foramen of Monro. This syndrome has been linked to mutations in the *TSC1* or *TSC2* genes, which drive tumor growth via the mammalian target of rapamycin (mTOR) signaling pathway.^{8,9}

Patients with Turcot syndrome exhibit multiple colonic polyps in association with intracranial neoplasms. This disorder results from mutations in the adenomatous polyposis coli (*APC*) gene and in DNA mismatch repair genes.¹⁰ Affected patients generally have malignant gliomas or primitive neuroectodermal tumors (PNETs). Several less common syndromes have also been linked anecdotally with glial neoplasms.

34.2 Pathology

Cerebral hemispheric low-grade gliomas are generally subdivided into several major groups, based on their presumed cell of origin.^{11,12} These groups include (1) astrocytic tumors, including pilocytic and nonpilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma; (2) oligodendroglial tumors; (3) mixed gliomas; and (4) benign neuroepithelial tumors, such as ganglioglioma, desmoplastic infantile ganglioglioma, and dysembryoplastic neuroepithelial tumor. Malignant gliomas are subdivided into anaplastic astrocytoma, mixed glioma or oligodendroglioma (grade III), and glioblastoma (grade IV). The appearances of the most common histologic subgroups of gliomas are illustrated in ► Fig. 34.1.

Daumas-Duport et al¹³ proposed a relatively simple grading system for nonpilocytic astrocytomas based on a limited number of histologic features. Lesions were given one point for each of the following factors: nuclear atypia, mitoses, endothelial proliferation, and necrosis. Grade 1 lesions had none of these characteristics, grade 2 had one, grade 3 had two, and grade 4 had three or four. Because these criteria generally appeared in sequence, grade 2 tumors were generally characterized by nuclear atypia, grade 3 by their mitotic activity, and grade 4 by the presence of either necrosis or endothelial proliferation. A modified version of this simplified scheme has been incorporated into recent World Health Organization (WHO) classification guidelines.¹²

Pilocytic astrocytomas are characterized by areas of compact bipolar astrocytes alternating with loosely packed areas containing microcysts. Macrocysts are also common. Eosinophilic granular bodies and Rosenthal fibers are characteristically seen. Occasional mitotic figures, leptomeningeal infiltration, and vascular proliferation do not appear to affect prognosis adversely, in contrast to the situation with nonpilocytic astrocytomas.

Pleomorphic xanthoastrocytomas arise most commonly in the temporal or parietal lobes and are often associated with a cyst. These lesions are characterized by pronounced nuclear atypia with pleomorphism and multinucleation in the setting of a low mitotic index. Abundant lipid-rich cells and pronounced reticulin reactivity, particularly in the regions of leptomeningeal invasion, are also typical. Approximately 20% of these lesions undergo malignant transformation, with pronounced mitosis, necrosis, and endothelial proliferation.^{3,12}

Subependymal giant cell astrocytomas arise near the foramen of Monro and contain large cells resembling astrocytes. Perivascular pseudopalisading is often seen, but mitoses are rare. Immunoreactivity for both glial and neuronal markers is often noted.

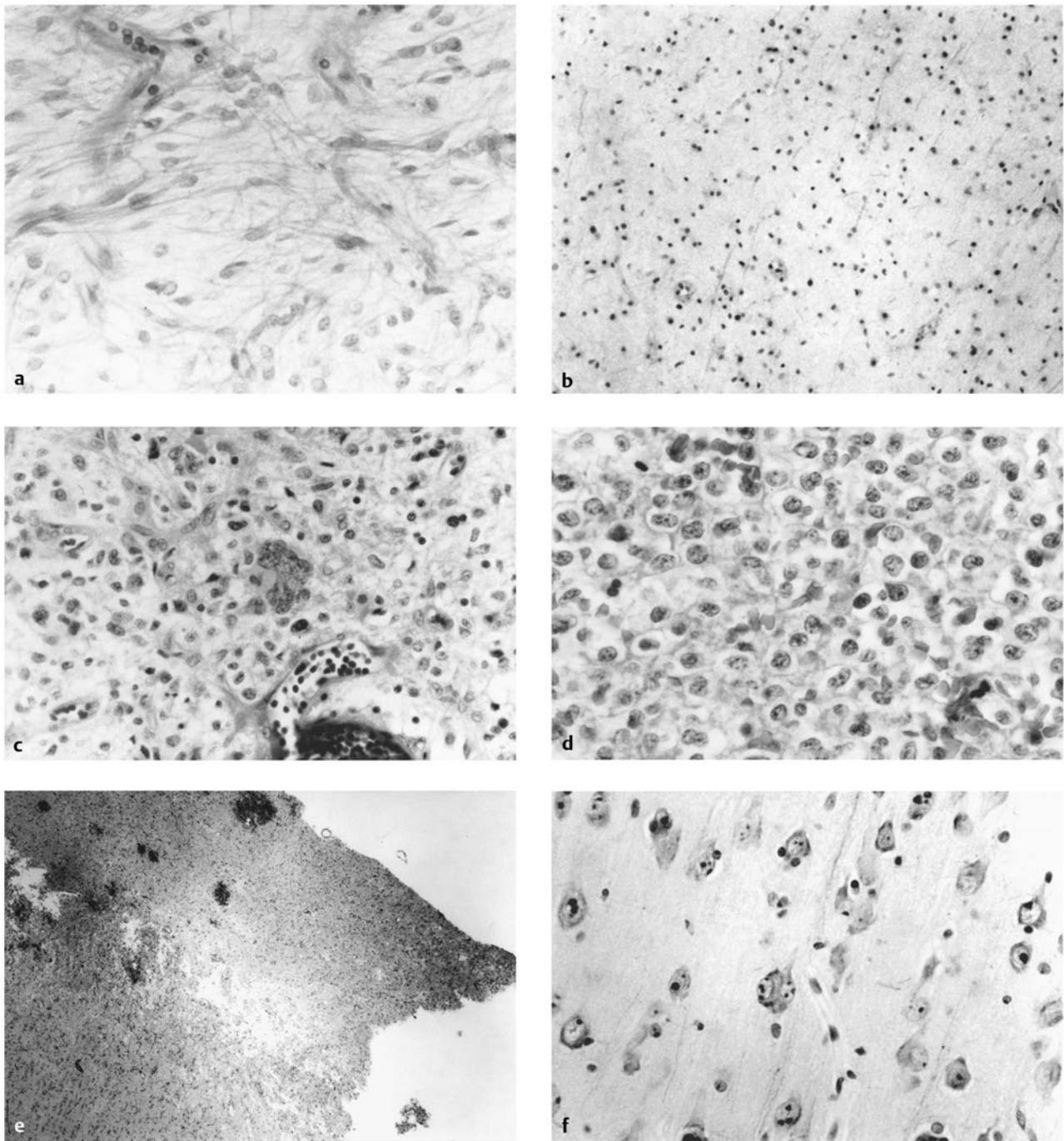


Fig. 34.1 Histologic appearance of common supratentorial hemispheric gliomas. (a) Pilocytic astrocytoma (hematoxylin and eosin [H&E]). Typical piloid (hairlike) processes with abundant Rosenthal fibers are apparent. (b) Nonpilocytic astrocytoma (H&E). This lesion exhibits monotonous sheets of minimally atypical neoplastic astrocytes, without mitosis or necrosis. (c) Malignant glioma (H&E). This specimen exhibits mitosis, necrosis, and vascular proliferation, all hallmarks of a glioblastoma multiforme. (d) Oligodendroglioma (H&E). The tumor is composed of cells that exhibit a characteristic “fried egg” appearance. (e) Mixed oligoastrocytoma (H&E). In this specimen, discrete foci of astrocytoma and oligodendroglioma are apparent, although in many lesions, the separation of such cell populations is less obvious. (f) Ganglioglioma (Nissl stain). Binucleated neoplastic neurons in a background of neoplastic astrocytes are illustrated.

Oligodendroglial tumors are characterized by spherical cells with hyperchromatic nuclei and a well-defined plasma membrane that gives a “fried egg” appearance. Focal calcifications are common. Lesions that exhibit a major astrocytic component, either diffusely or in distinct regions, are classi-

fied as mixed gliomas. Both oligodendrogliomas and oligoastrocytomas can exhibit features of anaplasia, with mitoses, necrosis, and vascular proliferation that, in some cases, may be difficult to distinguish from the features of glioblastoma multiforme.

Each of the benign neuroepithelial tumors has distinctive morphological characteristics. Gangliogliomas are characterized by the presence of neoplastic neurons with binucleation and atypia in a background of neoplastic astrocytes.¹⁴ Desmoplastic infantile ganglioglioma is notable for the young age of affected patients, the large size of the lesion, and the presence of a pronounced desmoplastic component containing a mixture of cells with astrocytic and neuronal differentiation.¹⁵ Finally, dysembryoplastic neuroepithelial tumor is notable for a cortical location, multinodular architecture containing neoplastic oligodendrocytes, neurons, and astrocytes, and an internodular neuroglial component, with neurons in a background of oligodendroglial cells.⁴

34.3 Molecular Pathogenesis

Recent studies have provided major insights into the molecular basis for pilocytic astrocytomas. A significant percentage of these tumors have alterations in the *BRAF* gene, either activating mutations, such as *BRAF* V600E, or translocations that produce a constitutively active variant, which leads to dysregulated signaling via the mitogen-activated protein kinase (MAPK) pathway.^{16–19} Similarly, dysregulation of mTOR signaling has been found to underlie the development of subependymal giant cell astrocytomas in tuberous sclerosis.^{8,9} In both cases, these consistent molecular alterations have provided a basis for logical strategies for molecularly targeted therapy. Studies of other pediatric gliomas have failed to demonstrate a consistent pattern of genetic abnormalities. Although adult low-grade gliomas frequently evolve secondarily into higher-grade lesions,^{20–23} this stepwise progression is less frequent in childhood gliomas, suggesting that there are fundamental differences between these groups. Adult grade II astrocytomas and the secondary malignant gliomas that arise from them commonly exhibit mutations in the *IDH1* or *IDH2* gene,^{22–24} whereas such mutations are uncommon in childhood lesions, with the exception of those arising in adolescence.²⁵ Likewise, adult lesions commonly have mutations in *TP53*; although these are found in a subset of childhood malignant gliomas, such mutations are rare in low-grade gliomas.²⁶ Childhood lesions are different from primary adult malignant gliomas, which are grade IV lesions at diagnosis; adult lesions characteristically exhibit deletions or mutations of the *PTEN* gene in association with amplification and/or rearrangement of the *EGFR* gene,^{23,27} whereas such abnormalities are observed in fewer than 10% of pediatric lesions.²⁸ However, recent studies indicate that a subset of pediatric malignant gliomas have amplification of the *PDGFRA* gene, or alterations of the *H3F3A* or *ATRX/DAXX* genes, suggesting that these tumors may have alternate pathways to gliomagenesis and thus may warrant distinctive therapeutic approaches.^{29,30,106}

One consistent finding in both childhood and adult malignant gliomas is the adverse association between overexpression of the DNA repair protein methylguanine-DNA methyltransferase (MGMT) and response to alkylating agents.^{31–33} Children treated with nitrosourea- or temozolomide-based regimens whose tumors have a low level of MGMT expression have a significantly better prognosis than those whose tumors show MGMT overexpression.^{32,33}

34.4 Clinical Presentation

Cerebral hemispheric gliomas characteristically present with seizures and focal neurologic deficits, such as hemiparesis, hemisensory deficits, and aphasia, depending on the site of the lesion and the age of the child (see box “Signs and Symptoms of Cerebral Hemispheric Gliomas”).³⁴ Whereas low-grade lesions often present with an insidious onset of symptoms over a period of months or with a long history of seizures, the mode of symptom progression in high-grade lesions is generally more rapid. Signs of increased intracranial pressure (ICP) and focal neurologic deficits are seen more commonly with high-grade lesions than with low-grade lesions. A small percentage of children present with sudden neurologic deterioration, which in most cases reflects intratumoral hemorrhage.

Signs and Symptoms of Cerebral Hemispheric Gliomas

- Common signs and symptoms
 - Seizures
 - Hemiparesis
 - Hemisensory deficits
 - Aphasia/dysphasia
 - Headaches
- Uncommon signs and symptoms
 - Vomiting
 - Macrocephaly
 - Failure to thrive
 - Papilledema
 - Lethargy

The characteristic mode of presentation for benign neuroepithelial tumors, such as ganglioglioma and dysembryoplastic neuroepithelial tumor, is with partial complex seizures that in many cases are refractory to anticonvulsant medications. Signs of increased ICP and focal neurologic deficits are infrequent. In many cases, seizures have been present for years before the diagnosis. However, desmoplastic infantile ganglioglioma is a notable exception to this general pattern. Because these tumors often arise during infancy and are large, affected patients commonly present with the gradual onset of macrocephaly and other signs of increased ICP, such as a bulging fontanel, “setting sun” eye sign, and failure to thrive.

In the past, subependymal giant cell astrocytomas characteristically manifested with symptoms of increased ICP secondary to ventricular dilatation from obstruction of the foramen of Monro or with seizures and hemiparesis from involvement of the overlying frontal cortex. With the widespread availability of high-resolution imaging techniques, such tumors are now often detected at a presymptomatic stage on screening neuroimaging evaluations of children with tuberous sclerosis.

34.5 Diagnostic Studies

Computed tomography (CT) or preferably magnetic resonance (MR) imaging is usually the only diagnostic study needed to establish the presence of a supratentorial hemispheric tumor (► Fig. 34.2). Low-grade astrocytomas are typically hypodense

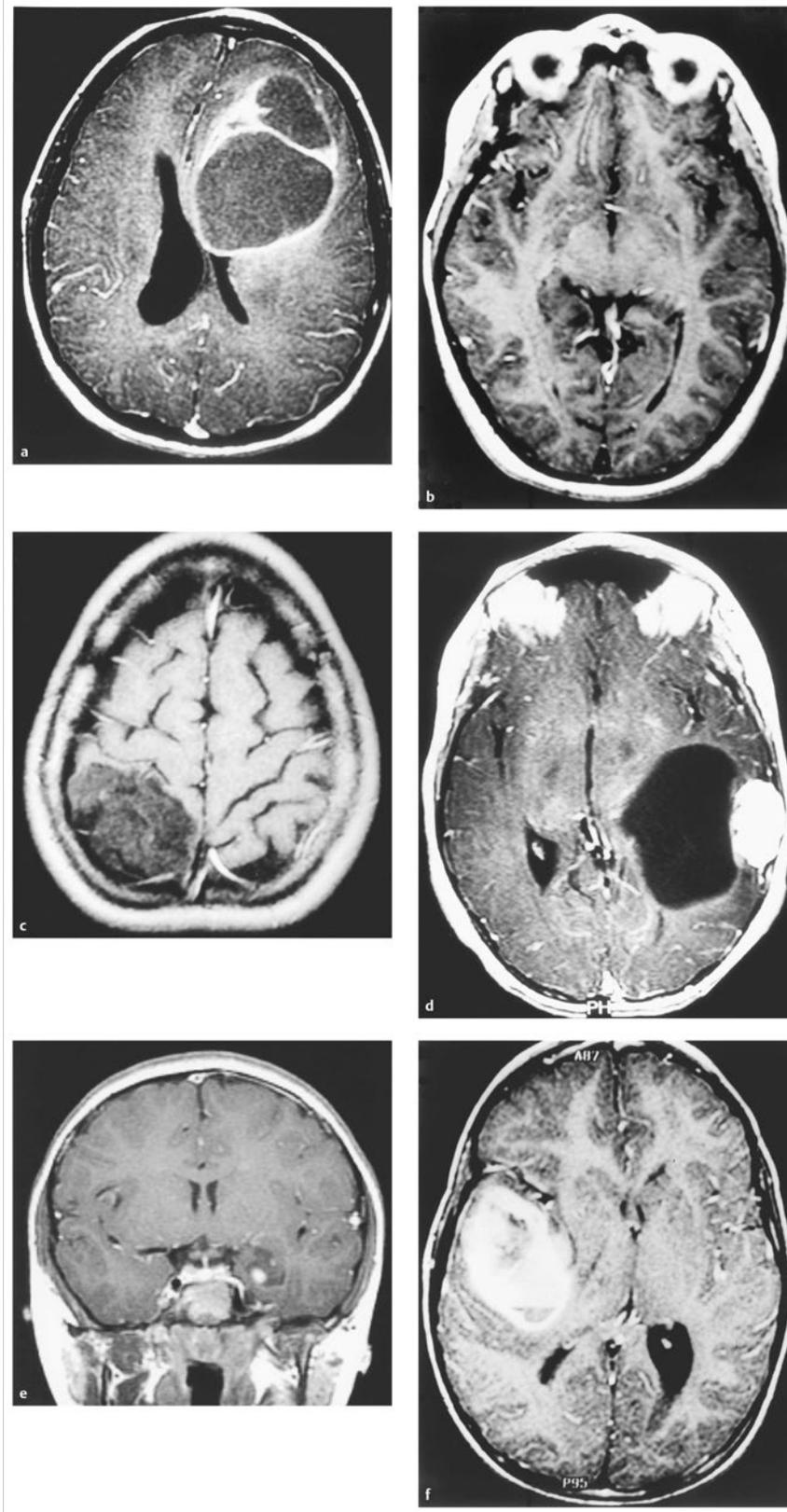


Fig. 34.2 Magnetic resonance images of common supratentorial hemispheric gliomas. (a) Pilocytic astrocytoma. (b) Nonpilocytic astrocytoma. (c) Oligodendroglioma. (d) Pleomorphic xanthoastrocytoma. (e) Dysembryoplastic neuroepithelial tumor. (f) Malignant glioma.

on a CT scan and hypointense on a T1-weighted MR image in comparison with the surrounding brain. Pilocytic tumors often exhibit well-defined borders with enhancement in the form of a mural nodule. However, a uniform or ringlike pattern of

enhancement is sometimes observed. In contrast, nonpilocytic tumors are often poorly delimited on a CT scan or T1-weighted MR image and appear as a poorly circumscribed area of increased signal on T2-weighted images. These lesions often show

little or no enhancement, but some cases closely resemble pilocytic tumors. Oligodendrogliomas and gangliogliomas may resemble either pilocytic or nonpilocytic astrocytomas but are more likely to show calcification; of the two, gangliogliomas are more likely to arise in the temporal lobe.

Pleomorphic xanthoastrocytomas characteristically arise at or close to the cortical surface in association with an underlying cyst. Enhancement of the solid tumor component is typically seen. Subependymal giant cell astrocytomas appear as well-circumscribed, homogeneously enhancing lesions located adjacent to the foramen of Monro and are often associated with obstructive hydrocephalus. Desmoplastic infantile gangliogliomas are characterized by their superficial location, which often extends to the leptomeninges, and their large size. These lesions are often partially cystic and have a densely enhancing solid component. Dysembryoplastic neuroepithelial tumors appear as well-demarcated, superficial lesions that are hypodense on CT and hypointense on T1-weighted MR imaging, giving a pseudocystic appearance. Enhancement, if present, is slight.

Malignant gliomas typically exhibit irregular or ringlike enhancement on CT and MR imaging, with a surrounding area of low density on CT, low intensity on T1-weighted MR imaging, and high intensity on T2-weighted MR imaging that represents infiltrating tumor and edema. Because these lesions grow more rapidly than low-grade gliomas, they often produce a substantially greater local mass effect. It is sometimes difficult to distinguish these lesions from other malignant hemispheric tumors, such as ependymomas and PNETs.

Other diagnostic studies are rarely needed preoperatively. Lumbar puncture should specifically be avoided because of the risk for herniation in the setting of a large mass lesion. Angiography is indicated only if a tumor exhibits unusual vascularity, in which case preoperative embolization may be considered, or if concern is raised that the lesion may be a vascular malformation. Neuraxis imaging is needed for only a subset of supratentorial tumors, such as PNETs, and unless this diagnosis is strongly suspected, it is typically reserved for the postoperative period after a histologic diagnosis has been obtained.

34.6 Surgical Treatment

34.6.1 Perioperative Management

Most children referred for neurosurgical evaluation have already had an adequate-quality MR imaging examination that is sufficient for operative planning. However, an additional imaging study suitable for intraoperative neuronavigation is sometimes needed, which helps both to localize the lesion and to assist with operative planning. The timing of operative intervention is largely determined by the condition of the child. Patients who present with obtundation from a large mass undergo resection on the day of admission. Children who have a large lesion but are minimally symptomatic undergo surgery on the next available operating day. Smaller lesions that present with seizures and minimal mass effect are treated on a more elective basis.

Corticosteroids are generally begun on admission in children with large tumors or are administered preoperatively in patients with smaller lesions at a dose in the range of 0.1 mg/kg every 6 hours (for dexamethasone). These are continued

intraoperatively and then tapered during a period of 3 to 7 days if significant tumor debulking has been achieved. Because children with hemispheric tumors may be at risk for seizures during the perioperative period, anticonvulsants are often begun preoperatively, even if the child has not previously had a seizure, and maintained for at least 1 week postoperatively. The use of longer courses of anticonvulsants in patients without a history of seizures is of uncertain benefit. In patients with a history of preoperative seizures, the duration of postoperative anticonvulsants is largely empiric. Many groups discontinue the anticonvulsants several months after surgery if the child has been rendered seizure-free. In view of the trend toward minimizing or avoiding hair shaving for neurosurgical procedures, an antibacterial shampoo on the night before surgery and on the morning of surgery is often employed to decrease skin and hair flora.

Because cerebral hemispheric gliomas rarely produce significant hydrocephalus, external ventricular drainage is normally not initiated preoperatively. In the occasional case in which a ventricle is partially trapped or expanded by tumor and the risk for perioperative hydrocephalus is a concern, a ventricular catheter may be placed intraoperatively and then withdrawn by gradually raising the drainage chamber during the first several days after the tumor resection. Few children require shunts as a part of their initial operative management.

34.6.2 Surgical Planning

In general, surgical intervention forms the initial step in the treatment plan by providing tissue with which to establish the histologic diagnosis and by achieving cytoreduction, if this is safely feasible. An important consideration in selecting the optimal approach to a supratentorial hemispheric lesion centers around developing a clear plan of the goals of the operation (e.g., biopsy, reduction of mass effect, gross total resection, and/or treatment of hydrocephalus), which are influenced by the growth characteristics of the tumor as depicted by CT or, preferably, MR imaging. Ideally, for well-circumscribed lesions, a gross total resection should be the operative goal, if this can be achieved without inordinate risk. This is feasible for most pilocytic astrocytomas, even if they arise in subcortical regions, for many superficial nonpilocytic astrocytomas and benign neuroepithelial tumors, and for some superficial high-grade gliomas. Because there appears to be a major prognostic advantage to obtaining a gross total or nearly total resection of these tumors,³³⁻³⁷ the extra risk involved in achieving this goal may be justified by the potentially improved outcome that can be realized.

Conversely, for some infiltrative, poorly circumscribed high-grade gliomas and nonpilocytic low-grade gliomas that cross the midline or extensively invade the deep nuclei and other critical brain regions, substantial resection may not be feasible without unacceptable morbidity. In small or highly diffuse lesions with minimal local mass effect, a percutaneous image-guided stereotactic biopsy may be preferable to an extensive open operation with limited tumor removal as a means for safely establishing a histologic diagnosis in preparation for adjuvant therapy. However, for large lesions with extensive mass effect and a well-defined "core" on imaging, an open biopsy combined with an aggressive subtotal resection may be of value

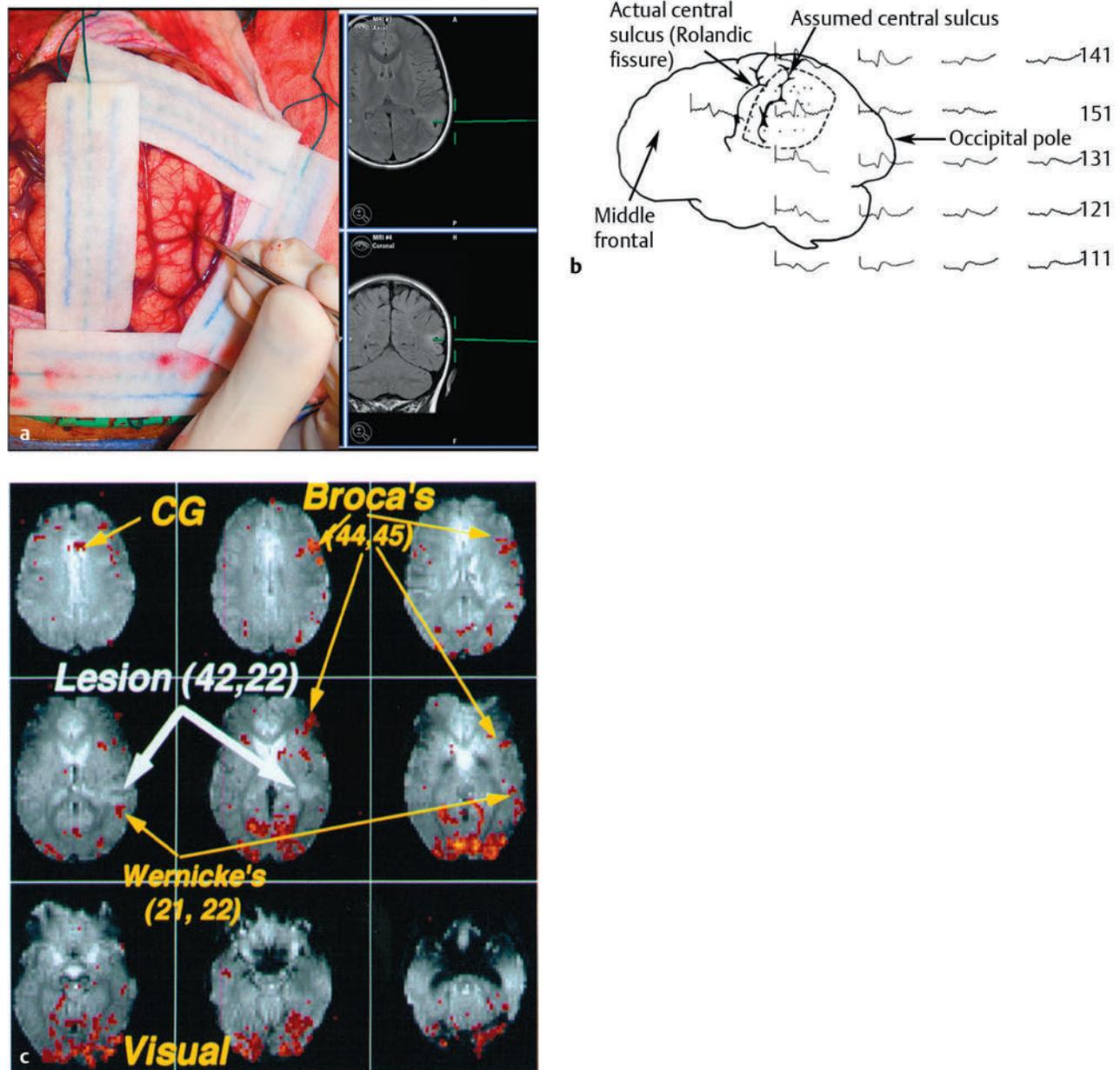


Fig. 34.3 Preoperative and intraoperative adjuncts that facilitate tumor resection. (a) Stereotactic localization with frameless navigation allows planning of the operative trajectory and facilitates anticipation of the tumor margins during the course of the resection. (b) Intraoperative somatosensory evoked potential mapping of the central sulcus, which, as illustrated here, is often displaced or distorted by a nearby tumor. In this case, the data recorded from a strip electrode positioned over the lesion, both posterior and anterior to the presumed central sulcus, all demonstrated a classic N20, P30 complex, suggesting that this region was actually parietal cortex. Only when the recording strip was advanced anterior to the lesion was an N20, P30 inversion consistent with motor cortex observed. (c) Functional magnetic resonance image mapping of speech functions, which, as illustrated here, are in close proximity to a dominant parietal tumor.

in stabilizing the patient in preparation for further treatment. In the latter circumstances, the goal should be to take out as much tumor as possible while minimizing the risk for neural injury.

Fortunately, several adjuncts have become available that facilitate the extensive removal of lesions previously thought to be unresectable, or resectable only with substantial morbidity (► Fig. 34.3). Stereotactic guidance systems allow preoperative and intraoperative localization of the tumor, which permits the

surgeon to choose an operative approach that minimizes the manipulation of functionally critical brain and maximizes the extent of resection that can be achieved (► Fig. 34.3a). Ultrasound and intraoperative MR imaging are also increasingly used to provide real-time feedback on the location of the lesion, which avoids problems with intraoperative brain movements that limit the accuracy of stereotactic techniques after the tumor resection has been initiated. However, particularly for MR imaging, the significant cost of an intraoperative scanner and

the lengthened operative times needed to apply this modality constitute drawbacks to more widespread application.

A variety of techniques have also been developed for the functional localization of critical brain areas in the vicinity of a superficial tumor or overlying a deep-seated lesion. For superficial lesions, these techniques enable the surgeon to resect as much tumor as possible without damaging vital surrounding structures, and for deep lesions, they allow the surgeon to choose a trajectory to the tumor that avoids traversing important loci. Cortical stimulation techniques,³⁸ which may be applied both extraoperatively, by means of grid or strip electrodes that have been implanted at a preliminary procedure, and intraoperatively, at the time of the planned tumor resection, are useful for identifying speech and motor areas. Although motor mapping can be accomplished in patients who are under general anesthesia, intraoperative speech mapping requires the patient to be awake, which generally limits the applicability of this technique to children older than 10 years. Accordingly, for younger patients, extraoperative mapping is preferable. Intraoperative somatosensory evoked potential recordings (► Fig. 34.3b) are also helpful for delineating the primary sensory cortex and central sulcus in an anesthetized patient, but in contrast to direct stimulation techniques, they are not useful for mapping subcortical pathways. Functional MR (fMR) imaging and diffusion tensor imaging offer alternative approaches for localizing critical cortical and subcortical areas and pathways before a tumor resection is begun (► Fig. 34.3c).^{39,40} This information can be integrated with stereotactic techniques to precisely delineate relevant loci around the tumor. Finally, in patients who have intractable seizures in association with cerebral cortical lesions, electrocorticography provides an opportunity for determining whether or not the seizures originate from the site of the lesion and for identifying epileptogenic cortex adjacent to or distant from the tumor to optimize the chances for postoperative seizure control.³⁸

34.6.3 Anesthesia, Positioning, and Surgical Approaches and Techniques

For hemispheric tumors that are appropriate candidates for open resection, the anesthetic technique, positioning, and surgical approach are determined by the location of the lesion and type of monitoring that is planned. The anesthetic technique generally consists of a mixture of fentanyl, vecuronium, nitrous oxide, and isoflurane. The approach is modified depending on the type of monitoring employed. For example, somatosensory evoked potential monitoring requires a reduction in the levels of inhalation agents, whereas motor mapping requires a limitation in the level of paralysis; the other agents are adjusted accordingly. Achieving reliable monitoring while keeping the patient appropriately anesthetized requires that the anesthesiologist be informed preoperatively of the surgeon's plans. Other common features of the surgical preparation include insertion of a urinary drainage catheter, arterial line, and, if significant blood loss is anticipated, a central line and sizeable peripheral intravenous lines. Prophylactic antibiotics are administered during the skin preparation and periodically during the procedure. Corticosteroids and anticonvulsants are also continued intraoperatively.

The positioning used for tumor resection is commonly supine or lateral decubitus, depending on the operative trajectory. A head fixation device is generally used for children older than 2 to 3 years, whereas a horseshoe headrest is commonly employed in younger patients. We currently avoid shaving large areas of the head; instead, we trim a 1- to 2-cm strip along the planned incision line and then scrub the hair and scalp with an antibacterial soap before a formal skin preparation.

For superficial cortical tumors and subcortical lesions that are not immediately beneath functionally essential cortex, the most direct trajectory to the lesion is usually appropriate (► Fig. 34.4). However, for subcortical lesions that are beneath critical brain regions, stereotactic and/or functional mapping techniques, such as fMR imaging and diffusion tensor imaging, coupled with direct mapping, are useful for selecting the safest approach to the tumor. These strategies are particularly valuable for lesions that arise from or extend into the thalamus and basal ganglia. The approach to these deep subcortical lesions is also influenced by the predominant direction of tumor growth. Lesions that grow medially and encroach on or expand within the lateral ventricle can be approached transcally or transfrontally, whereas tumors that extend laterally in the nondominant hemisphere may be approached through the insula after the sylvian fissure has been opened. Laterally extending lesions within the dominant hemisphere and tumors that arise more posteriorly within the thalamus may be reached via a posterior parietal approach situated behind the sensorimotor cortex and above the angular gyrus. Selected lesions can also be reached via an occipital trajectory. Finally, tumors that project anterolaterally can be reached from a paramedian frontal trajectory, provided that care is taken to avoid injury to the motor pathways.

The skin incision is determined by the location of the lesion, with a question mark, C-shaped, or linear incision for temporal lesions; a bicoronal incision for low frontal lesions; and a linear or C-shaped incision for posterior frontal, parietal, or occipital lesions (► Fig. 34.4). The bone removal and dural opening are performed in a standard fashion.

In most cases, we obtain a frozen section diagnosis after the tumor has been exposed because this information sometimes influences subsequent intraoperative management. For example, for certain diagnoses, particularly ependymoma, the extent of resection has such an overwhelming impact on the prognosis that we are more willing to risk causing a minor neurologic deficit if it will permit a complete resection. Conversely, for a diagnosis of malignant glioma, in which a truly complete resection is not feasible because of the inherent invasiveness of the tumor, we also make a concerted effort to remove the central tumor mass, but we would not "chase" the lesion into surrounding infiltrated brain tissue.

The actual tumor resection is usually initiated with the use of ultrasonic aspiration to debulk the center of the lesion. Some low-grade gliomas, particularly pilocytic tumors, have a well-delineated peritumoral plane through which the neoplasm can be separated from the surrounding brain after the central portion of the mass has been debulked. With most nonpilocytic gliomas and high-grade gliomas, no such plane is observed, and the resection must proceed cautiously from the inside outward until a boundary between tumor and normal brain is reached. As previously noted, this boundary may be indistinct with

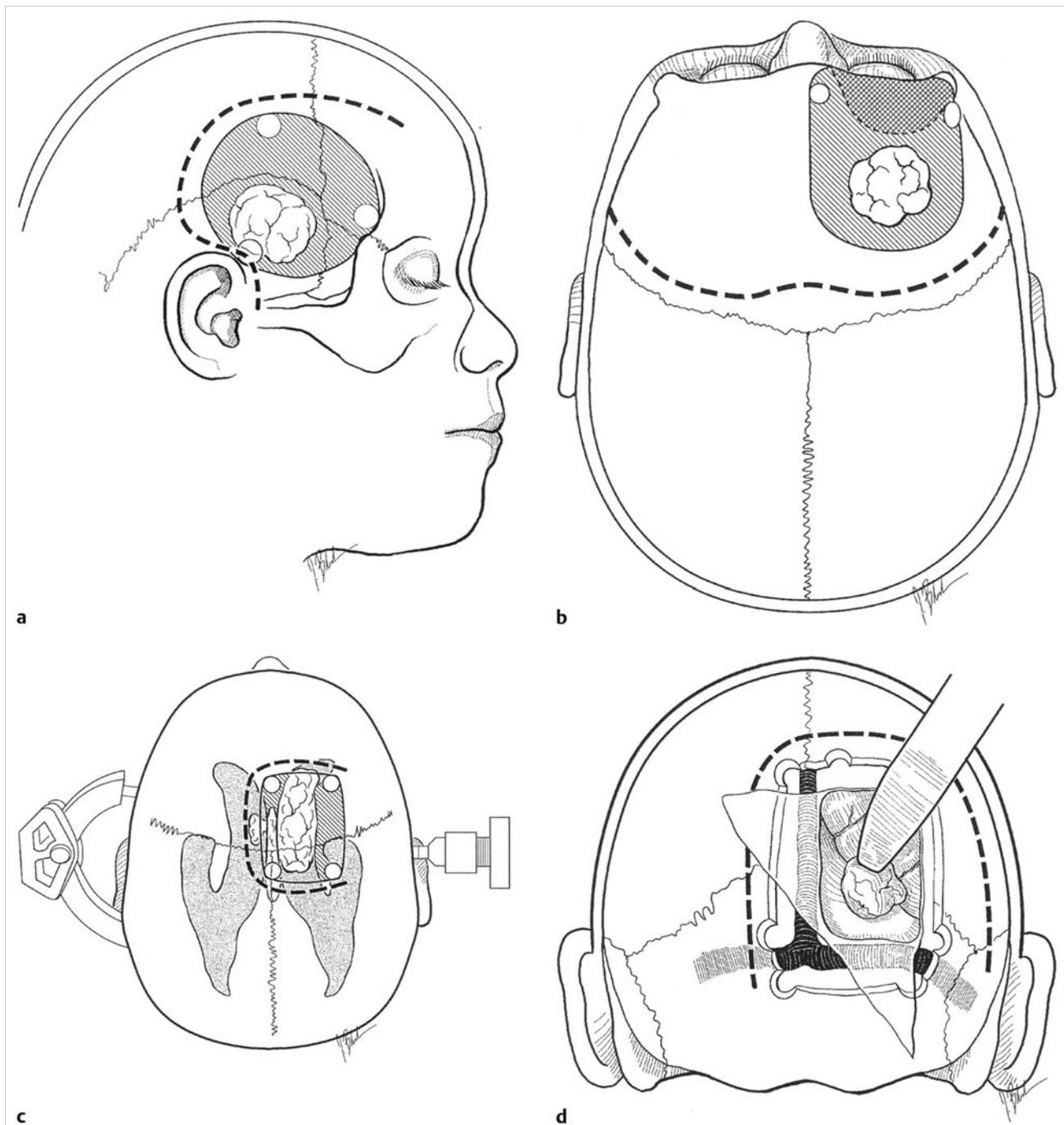


Fig. 34.4 Skin incisions (indicated as dashed lines) and operative approaches for supratentorial hemispheric lesions in various locations. (a) Temporal lesion. (b) Low frontal lesion. (c) Medial hemispheric or intraventricular lesion. (d) Occipital lesion.

infiltrative lesions, and a complete resection may be impossible without unacceptable morbidity.

An important caveat in attempting to achieve a gross total resection concerns the management of cystic low-grade gliomas. For lesions with a well-defined mural nodule in which the cyst lining is nonenhancing and translucent, resection of the wall is unnecessary.⁴¹ In contrast, for lesions in which the wall is thick and enhancing, removal of this component of the tumor is essential, if feasible, to optimize the chances for disease control.

Similarly, pleomorphic xanthoastrocytoma and desmoplastic infantile ganglioglioma often show extensive attachment to the leptomeninges, which (if safely feasible) should be removed along with the tumor to minimize the risk for recurrence. The large size and dense vascularity of desmoplastic infantile gangliogliomas and their typical origin in infants mandates that particularly close attention be directed to obtaining adequate arterial and central venous monitoring and intravenous access before the resection is begun, and to ensuring appropriate

blood and clotting factor replacement, because death from hypovolemia or coagulopathy has historically been a significant risk.⁵

A final point in the overall surgical plan concerns the importance of postoperative imaging to determine the extent of resection. For virtually all types of pediatric hemispheric gliomas, the extent of residual disease is a major predictor of outcome. In this context, if the initial operation was undertaken with the goal of achieving a gross total tumor removal and postoperative imaging discloses that a potentially resectable lesion has inadvertently been incompletely removed, consideration may be given to embarking on another attempt at gross total resection before proceeding with any adjuvant therapy.

34.7 Outcome, Prognostic Factors, and Adjuvant Therapy

34.7.1 Low-Grade Pilocytic and Nonpilocytic Astrocytomas

Studies indicate that the three most important determinants of outcome in children with low-grade cerebral hemispheric astrocytomas are tumor histology, extent of resection, and tumor location (superficial vs. deep). However, these factors are all interrelated, which has complicated efforts to confirm that any single factor is independently predictive of outcome. For example, it is generally held that children with pilocytic astrocytomas have a better prognosis than those with nonpilocytic low-grade gliomas. However, a confounding factor that favors better outcomes with pilocytic tumors is that these lesions are generally well circumscribed and amenable to gross total resection, which is less often the case with nonpilocytic gliomas. Because resection extent is strongly associated with outcome for low-grade gliomas,^{20,34,36,37} it has been difficult, based on

previous studies, to exclude the possibility that pilocytic tumors have a better outcome simply because of their increased resectability. In this regard, results of a large natural history study from the Children's Cancer Group (CCG9891) and Pediatric Oncology Group (POG8930) in more than 500 patients highlighted that outcome was most significantly influenced by resection extent, independently of histology.³⁷

A related issue is whether resection extent is the direct cause of the more favorable outcomes of certain low-grade gliomas, or whether tumors that are amenable to gross total resection (by virtue of their well-circumscribed growth characteristics) merely represent an inherently more favorable biological group. Because there is no ethical way of settling this issue in a randomized format, it will continue to be difficult to prove that resection extent is the primary *determinant* of outcome in childhood gliomas, rather than merely a *correlate* of outcome. In this context, deep-seated (e.g., thalamic) gliomas have historically had a worse outcome than more superficial hemispheric lesions,³⁷ which may simply reflect that the former tumors are more difficult to resect completely or, alternatively, that these lesions constitute a biologically more aggressive group.

The above issues notwithstanding, there is sufficient indirect evidence to support the concept that complete resection of low-grade gliomas of childhood is a worthy operative goal, if safely attainable (► Fig. 34.5). After an extensive resection, with removal of radiologically detectable tumor, the 5-year progression-free survival (PFS) rate exceeds 75%, and in many studies, it approaches 100%.^{34,36,37,42,43} By comparison, the 5-year PFS rate for children with incompletely resected tumors not treated with radiotherapy is approximately 50 to 80%.^{34,37,42} However, the overall 5-year survival rate for children with subtotaly resected low-grade gliomas exceeds 90%, which is substantially better than results observed in adults.^{20,21,34,37,42} In large measure, this reflects that progressive low-grade gliomas in adults commonly exhibit malignant degeneration.^{20,21} This

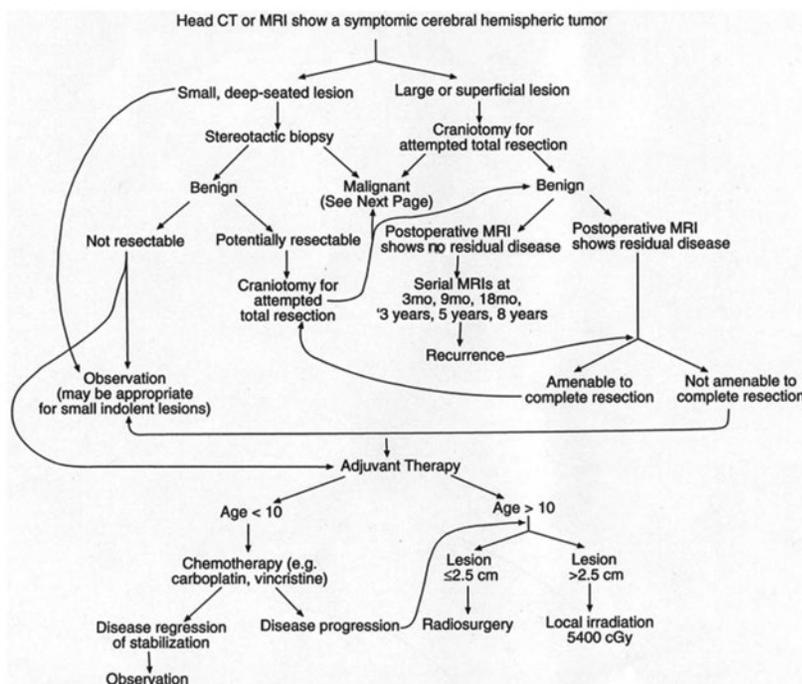


Fig. 34.5 Management protocol for low-grade hemispheric gliomas. CT, computed tomography. MRI, magnetic resonance imaging.

phenomenon occurs less frequently in pediatric low-grade gliomas, which generally remain histologically benign at progression and respond well to additional therapeutic approaches.³⁴ The striking difference in overall outcome between children and adults with low-grade gliomas probably results from differences in the biological characteristics of the tumors in these two age groups.

The value of radiotherapy for patients with low-grade hemispheric gliomas has long been a subject of controversy. Although a beneficial effect of radiotherapy on survival has been detected in adult patients with subtotally resected low-grade gliomas,^{20,44} a survival advantage is less clear for adults undergoing gross total tumor resection or for children undergoing total or nearly total tumor removal.⁴⁵ Efforts to address this issue in a randomized format have been complicated by difficulties with patient accrual. However, in view of the generally favorable outcomes of children who have undergone gross total tumor resection, there is little rationale to proceed with adjuvant therapy. A similar argument has been made for children who have had extensive subtotal tumor removal because many patients remain free of progression for extended periods. In those with progression, the tumor can often be completely resected at a subsequent operation.^{34,36,37,46} In our institutional series, the use of radiotherapy after an initial incomplete resection had a significant impact on PFS but had no influence on overall survival.³⁴ With a median follow-up of more than 8 years, 6 of 33 patients who received radiotherapy had disease progression, compared with 7 of 16 patients not receiving radiotherapy ($p=0.014$). Overall survival, however, was actually better in the latter group because three of the patients who received irradiation developed malignant lesions within the treatment fields, a change observed in none of the patients who did not receive irradiation.

The observation that pediatric low-grade gliomas may remain quiescent after an incomplete resection suggests that a subgroup of tumors exhibits decelerating growth kinetics over time, which fits with recent observations that tumor cells with *BRAF* alterations may undergo senescence after an initial period of growth.¹⁹ In view of this biological variability, many surgeons prefer to follow patients with small amounts of residual disease in an expectant fashion, intervening only in the event of tumor progression. In such cases, re-exploration and complete resection are sometimes feasible^{34,36,46}; if not, adjuvant therapy may then be employed.

A further rationale for deferring radiotherapy after an initial aggressive resection is based on the potential morbidity of this therapy. First, it has been observed anecdotally that incompletely resected gliomas that have been radiated seem to show an increased incidence of malignant transformation,^{34,47} although this may reflect an underlying predisposition of such tumors. Second, external beam radiotherapy has known risks to the developing nervous system in the form of cognitive delay, endocrinopathies, and vasculopathy.^{48–50} Accordingly, chemotherapy is often used to defer irradiation in young children. Although this approach has been applied most extensively in children with unresectable midline tumors, such as chiasmatic-hypothalamic gliomas,⁵¹ favorable results have also been

obtained in children with unresectable hemispheric tumors. A variety of chemotherapeutic approaches have been utilized for these tumors.^{51–53} The efficacy and tolerability of two regimens, carboplatin–vincristine and 6-thioguanine–procarbazine–lomustine–vincristine, were recently compared in the A9952 study of the Children’s Oncology Group and a follow-up study (ACNS0223) that built upon the carboplatin–vincristine regimen by adding temozolomide, another potentially active agent. Results from the latter study are pending at this time. Recent studies have also examined biological therapeutics, including antiangiogenic agents such as bevacizumab and lenalidomide, and agents directed against the dysregulated growth signaling pathways observed in these tumors.^{8,9,54}

Alternate strategies that have been applied to treat foci of unresectable tumor include stereotactic radiosurgery^{55,56} and interstitial radiotherapy,⁵⁷ in which a high dose of radiation is administered to a precisely defined location, thereby minimizing exposure of the surrounding normal brain to radiation. Because radiosurgery provides treatment in a single fraction without the need for an open operation, this approach has been more widely applied. Although preliminary results with both techniques are encouraging, more extended follow-up will be needed to determine whether these approaches are truly beneficial in terms of prolonging long-term PFS and avoiding the potential for late malignant transformation.

The above alternatives notwithstanding, conventional radiation remains a worthwhile option for children older than 10 to 12 years with large areas of unresectable disease, in whom the risks for morbidity may be lower.⁴⁹ New methods of delivering fractionated radiotherapy in a conformally oriented treatment field with three-dimensional image-based treatment planning and narrow peritumoral margins have been developed to minimize treatment-induced morbidity without sacrificing disease control.^{58,59} This approach is currently being evaluated in further detail in a cohort of children in the Children’s Oncology Group ACNS0221 study.

An additional issue that is critical in defining the functional outcome of children with hemispheric low-grade astrocytomas is seizure control. Because many patients present with seizures and a sizeable subgroup have intractable epilepsy, measures directed at achieving postoperative seizure control are of significant therapeutic importance. The merits of *lesionectomy* versus formal epilepsy operations remain a subject of some debate. Several groups have reported favorable results in terms of seizure control after simply resecting the tumor.^{36,60} Others, however, have noted that patients with long-standing, medically intractable seizures benefit from perioperative and intraoperative mapping of seizure foci to guide a more extensive resection to achieve long-term seizure control without medications.^{38,61,62} Our preference has been to use thorough preoperative noninvasive and, if needed, invasive monitoring with subdural grid and strip electrodes to localize epileptogenic foci before undertaking tumor resection in patients with medically intractable epilepsy in association with a cortical tumor. This information is typically supplemented by intraoperative postresection electrocorticography to facilitate the removal of potentially epileptogenic cortex near the tumor, if safely feasible.

34.7.2 Pleomorphic Xanthoastrocytomas

These tumors typically have a favorable long-term prognosis, with an actuarial survival of approximately 90% at 5 years and almost 80% at 10 years. However, several histologic factors appear to adversely influence outcome, including necrosis and increased mitotic activity.^{3,63,64} Several studies have noted that extent of resection has the strongest association with outcome; long-term survival has been reported in 90% of patients undergoing gross total resection versus 65% of those undergoing incomplete resection.^{64,65} Tumors that recur after an initial resection may show evidence of more anaplastic features at reoperation, indicating that these lesions exhibit a potential for malignant progression. Because the value of adjuvant radiotherapy for incompletely resected lesions remains uncertain,^{3,64} there is a rationale to avoid irradiation initially and to repeat resection in children who subsequently develop disease progression (► Fig. 34.5).

34.7.3 Subependymal Giant Cell Astrocytomas

This highly characteristic tumor type arises in children with tuberous sclerosis. Most lesions are indolent and require treatment only if they attain a large size or obstruct the ventricular system. Because these tumors may have an abundant vascular supply and deep venous drainage, significant morbidity can result from attempts to remove them, and care must be taken in achieving meticulous hemostasis and avoiding inadvertent occlusion of major venous tributaries. The prognosis for long-term disease control is excellent after total or nearly total resection⁶⁶ (► Fig. 34.5). If a free communication between the lateral and third ventricles can be obtained, such patients often remain shunt-independent. In contrast, subtotally resected lesions do show a propensity to enlarge over time.⁶⁷ However, patients rarely die because of progressive tumor growth; many such lesions can be extensively resected at a subsequent operation. Radiotherapy or stereotactic radiosurgery has been used anecdotally for the management of unresectable recurrent lesions, but the long-term efficacy of these approaches is uncertain. More recently, the use of molecularly targeted therapy against the dysregulated mTOR signaling that characterizes these tumors has demonstrated a high rate of disease response and short-term tumor control,^{8,9} although the long-term efficacy of this approach as an alternative to surgery remains to be defined.

34.7.4 Oligodendrogliomas and Mixed Oligoastrocytomas

Oligodendrogliomas and mixed oligoastrocytomas of childhood show many similarities to astrocytomas in terms of their often indolent natural history and their favorable response to surgical therapy. Lesions that are well circumscribed are amenable to complete resection and are associated with an excellent long-term prognosis in children, which exceeds the outcomes observed in adults.^{34,68–70} The 5-year survival rate is in the range of 90%. For subtotally resected lesions, the benefit of

radiotherapy versus expectant management remains uncertain. Several groups have reported that incompletely resected oligodendrogliomas of childhood show a low incidence of disease progression.^{34,68} The use of involved-field conventional radiotherapy in patients with postoperative residual disease remains controversial. Because of the uncertain benefits of radiotherapy and the potential risks, our own preference has been to follow children who have known residual disease with serial scans. Further intervention is reserved for those patients who exhibit tumor progression (► Fig. 34.5). Because oligodendrogliomas that manifest with seizures often have an indolent course,^{68,69} long-term follow-up of such patients is often required to rule out progression. In contrast, lesions that present with intracranial hypertension or severe neurologic deficits may have a more aggressive course and account for the small subgroup of oligodendrogliomas that progress over time to higher-grade lesions. Tumors that have anaplastic features at diagnosis generally follow a rapidly progressive course and warrant postoperative therapy with a combination of adjuvant chemotherapy and radiotherapy, as described later for malignant gliomas.^{69,72–74} Although deletions of chromosomes 1p and 19q have been associated with a favorable response to adjuvant therapy in adults with these tumors,^{72,73} no such correlation has been apparent in childhood lesions.⁷⁵

34.7.5 Gangliogliomas and Benign Neuroepithelial Tumors

Because these lesions are usually well circumscribed, complete resection can often be achieved, and the 5-year survival rate exceeds 90%.^{37,76} The efficacy of radiotherapy for incompletely resected benign gangliogliomas remains unclear. Because these lesions tend to be extremely indolent, adjuvant therapy is probably appropriate only for those tumors that subsequently progress and are felt to be unresectable (► Fig. 34.5).⁷⁷

Dysembryoplastic neuroepithelial tumors are also indolent lesions with a favorable long-term outcome. These tumors are generally well circumscribed and often are amenable to complete resection. However, even after an incomplete resection, long-term PFS is common, and adjuvant therapy is often deferred.⁴ Because both gangliogliomas and dysembryoplastic neuroepithelial tumors often present with intractable epilepsy,^{76,78} postoperative seizure control is an important element in evaluating long-term functional outcome. As with supratentorial low-grade astrocytomas, preoperative and intraoperative measures to localize and resect epileptogenic foci in the vicinity of the tumor may have a role in improving ultimate seizure control.⁷⁸

In contrast to the above groups of tumors, which frequently manifest with a seizure disorder, desmoplastic infantile gangliogliomas often present with symptoms of increased ICP resulting from rapid tumor growth. Although complete resection of these well-circumscribed lesions is the therapeutic goal and is associated with a favorable prognosis for long-term PFS,^{79,80} their large size and profuse vascularity may necessitate a subtotal resection in certain cases. Because incompletely resected lesions often progress, several groups have favored administering adjuvant chemotherapy to patients with obvious residual

disease.⁵ This issue is controversial, however, and other groups advocate expectant management and re-exploration in the event of tumor progression because spontaneous regression of the residual tumor has sometimes been observed.^{81,82}

34.7.6 High-Grade Gliomas

These lesions have conventionally been treated with maximal resection followed by radiotherapy to the tumor bed and a margin of surrounding brain, with a dosage of 5,000 to 6,000 cGy in fractions of 180 to 200 cGy/d. The median survival rate for children with these tumors is in the range of 12 to 42 months, with a PFS of only 7 to 18 months.^{33,35,83–86} In recent studies using contemporary classification guidelines for eligibility, fewer than 20% of children have survived for 5 years without disease progression,^{33,84} a decrease compared with historical studies that used less rigorous entry criteria.^{35,86,87}

Adjuvant chemotherapy appears to have some utility in improving the chances for long-term survival, although the optimal treatment regimen remains to be determined. In a prospective controlled study (CCG-943), children who received radiation followed by lomustine, vincristine, and prednisone had a 5-year event-free survival (EFS) rate of 46% versus 18% for patients treated with radiotherapy alone.⁸⁶ In a subsequent study (CCG-945), a more complex eight-drug regimen failed to improve survival further.³⁵ It was presumed to reflect that the dose intensity of several components of the “eight-in-one” experimental regimen was low. This provided the impetus for a series of subsequent studies that examined the efficacy of more intensive regimens. In many cases, chemotherapy in a neoadjuvant (before irradiation) format was applied, or highly intensive regimens that coupled marrow-ablative chemotherapy with autologous bone marrow or peripheral blood stem cell reconstitution were employed. Although some studies suggested an improvement in outcome with this approach,⁸⁸ the results were less convincing in others, and the increased toxicity compared with conventional chemotherapy dampened enthusiasm for this strategy.⁸⁹ Subsequently, CCG-9933 compared three submyeloablative regimens, combining etoposide with either carboplatin, ifosfamide, or cyclophosphamide, but noted an unacceptably high rate of early disease progression, with a PFS rate of 15% at 24 months.⁸⁴ Results with several other neoadjuvant regimens in other cooperative group trials were equally disappointing.

In view of these results, subsequent studies have focused on attempting to enhance the efficacy of postradiation chemotherapy by administering active agents concurrently with irradiation. The ACNS0126 study administered temozolomide daily during irradiation and on a cycle of 5 days per 28 days after irradiation, patterned after the positive results obtained in an adult trial with this approach.^{31,90} Although the results in the pediatric trial were comparable with those in the adult study, they were no better than those in historical trials in which lomustine and vincristine were used.^{33,35,91} A subsequent study, ACNS0423, added lomustine to the postradiation component of therapy, although it remains to be determined whether outcome results were improved.⁹²

Despite the relatively limited advances that have been made in the adjuvant management of malignant gliomas, cooperative

group studies have provided useful information from the surgical perspective, calling attention to an association between resection extent and outcome. In the CCG-945 study, the 3-year EFS rate was 54% for patients undergoing tumor resection of more than 90% versus 17% for patients undergoing biopsy.⁹³ However, it was impossible to exclude the possibility that certain tumors with more favorable biological characteristics were inherently more amenable to extensive resection. In that regard, a subset of childhood malignant gliomas, particularly those occurring in infants, are sufficiently well circumscribed to be amenable to gross total resection,^{83,94} suggesting that they may be biologically distinct from more typical malignant gliomas.

An additional factor that has been associated with outcome in childhood malignant gliomas is tumor histology; patients with glioblastoma multiforme fare worse than those with anaplastic astrocytoma, with 5-year EFS rates in the range of 10% and 20%, respectively.^{35,86,87} Several studies have also noted that anaplastic gliomas with a substantial oligodendroglial component have a more favorable outcome than predominantly astrocytic malignant gliomas.³⁵ This may partially result from a greater sensitivity of the mixed lesions to conventional chemotherapeutic agents, such as the combination of procarbazine, lomustine, and vincristine. As noted earlier, chemosensitivity in adult oligodendroglial tumors appears to be selectively observed in lesions that exhibit deletions involving chromosomes 1p and 19q,^{72,73} although this correlation has not been confirmed in pediatric lesions.⁷⁵ Other molecular features, such as MGMT overexpression,^{32,33} TP53 mutations or overexpression,^{26,95} and high proliferation indices,⁹⁶ have been adversely associated with prognosis independently of histology.

The predominant site of disease progression for supratentorial malignant gliomas is at the primary site, which may be amenable to treatment by additional local therapy, such as surgical resection or stereotactic radiosurgery, followed by adjuvant chemotherapy. Despite aggressive therapy, the prognosis for long-term survival in such children is poor, reflecting the failure of current therapies to substantially slow the course of tumor growth in most patients. Cerebrospinal fluid dissemination of tumor is detected in as many as one-third of such children,⁹⁷ which further lowers the chances for achieving disease control. Improvements in the outcome of these patients will depend on identifying and implementing novel therapeutic approaches that target the molecular pathways that are aberrantly activated in these tumors. Although studies to date in which therapies targeted at both epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) have been disappointing,^{98,99} novel agents attacking other signaling mediators, such as PI3K and Akt, are currently under evaluation. An alternative approach involves directly targeting cell surface receptors that are uniquely expressed by glioma cells versus normal brain via the convection-enhanced delivery of immunotoxins directly into the tumor bed and peritumoral brain.¹⁰⁰ In addition, strategies to induce host immunologic responses against malignant gliomas have yielded promising preliminary results in both adult and childhood gliomas, and multi-institutional pediatric trials are under development.^{101–105}

Pearls

- Cerebral hemispheric tumors of childhood differ from those of adulthood in terms of their histologic distribution.
- There is a strong association between extent of resection and outcome for virtually all types of pediatric hemispheric tumors, including malignant lesions.
- An important consideration in selecting the optimal approach to a supratentorial hemispheric lesion centers on developing clear goals of the operation (e.g., biopsy, reduction of mass effect, major cytoreduction, and/or treatment of hydrocephalus), which are influenced by the growth characteristics of the tumor as depicted by CT or preferably MR imaging.
- For patients with well-circumscribed hemispheric tumors, a gross total resection should be the operative goal, if this can be achieved without inordinate risk.
- Several adjuncts have become available during the last several years, including neuronavigation, intraoperative imaging, and neurophysiologic monitoring, that facilitate the extensive removal of lesions previously thought to be unresectable, or resectable only with substantial morbidity.
- After a gross total or nearly total resection, low-grade gliomas can be managed expectantly; adjuvant therapy is reserved for the small percentage of tumors that progress. In contrast, high-grade lesions require intensive multimodality treatment after surgical resection.

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35 Supratentorial Nonglial Hemispheric Neoplasms

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Supratentorial non-midline tumors of nonglial origin are a diverse group of neoplasms and constitute a substantial proportion of all childhood brain tumors. The incidence of those that are not glial in origin (i.e., astrocytomas, ependymomas, others) is difficult to assess, which is due, in part, to our evolving understanding of the molecular infrastructure of these tumors, their postulated cells of origin, and—ultimately—one's definition of what is a glial versus a nonglial tumor. For example, should gangliocytomas be considered neural or glial tumors? Supratentorial tumors in general represent 22 to 54% of all pediatric brain tumors, and of these, about half are glial in origin; the remaining nonglial tumors are an interesting collection of many different types of pediatric brain tumors.^{1–5} Primitive neuroectodermal tumors (PNETs) represent about 5 to 10%, as do gangliogliomas, whereas other tumors occur in the 1 to 2% range and include choroid plexus papillomas/carcinomas (CPPs/CPCs), teratomas, dysembryoplastic neuroepithelial tumors (DNETs), meningiomas, germinomas (excluding those in pineal and suprasellar locations), sarcomas/chondromas, metastatic lesions, and lymphomas. Again, accurate statistics are difficult to obtain as these data are gleaned from case reports and from parts of larger mixed-case series. Nonetheless, unusual tumors occur in the supratentorial location and should be considered while treatment is being planned.^{1–3,5,6}

This chapter focuses on the main nonglial hemispheric tumors, including PNET, ganglioglioma/gangliocytoma/desmoplastic infantile ganglioglioma, DNET, CPP/CPC, meningioma, and—briefly—other rare tumors, such as central neurocytoma, germ cell tumors, metastatic malignancies and lymphoma.

35.1 Supratentorial Primitive Neuroectodermal Tumors

Supratentorial PNET is a relatively rare but challenging diagnosis that accounts for approximately 2.5 to 6% of all pediatric tumors.⁷ These tumors have a propensity for rapid growth, and thus the duration of symptoms is usually relatively short. The symptoms often include nonlateralizing signs of elevated intracranial pressure. Compared with medulloblastoma (the infratentorial equivalent of supratentorial PNET), supratentorial PNET has consistently demonstrated a worse prognosis, with 5-year survival rates ranging from 30 to 75% despite maximal therapy.^{7–12} These rates suggest an intrinsic biological difference between supratentorial and infratentorial PNETs.¹³ Originally, the etiologic cell of origin for PNETs was considered to be a primitive neuroepithelial cell capable of differentiating into neuronal, glial, and ependymal cell lines. The expression of *SOX2*, *NOTCH1*, and *ID1* is upregulated and the *JAK/STAT3* pathway is activated in supratentorial PNET, indicating a glial tumorigenesis. Conversely, the activation of proneural bHLH transcription factors is upregulated in infratentorial PNET, indicating a neuronal tumorigenesis.^{14–16}

35.1.1 Imaging and Preoperative Evaluation

PNETs are generally hyperdense on computed tomography (CT) and isointense (or hypointense) to brain on magnetic resonance (MR) imaging, with avid—but often heterogeneous—enhancement (► Fig. 35.1). A recent study of PNETs in children (i.e., patients younger than 20 years of age) suggests that there is about a 15 to 20% incidence of nonenhancement. The center of the tumor is often heterogeneous, with cysts and/or areas of necrosis.^{17–19}

Staging should be performed preoperatively by imaging the entire neuraxis. At initial presentation, 10 to 20% of patients will have disseminated disease.^{9,20–22} Lack of dissemination by imaging should be confirmed by cerebrospinal fluid (CSF) cytology analysis, but this is usually done postoperatively once the mass lesion has been removed.²³

35.1.2 Treatment and Outcome

PNET requires multimodal therapy, including surgical extirpation, craniospinal irradiation, and chemotherapy. Traditionally, all patients with supratentorial PNET were categorized as having high-risk disease, and survival rates have been less than 50% in most studies. Recently a multi-institutional group has stratified patients into average- and high-risk groups based on the following: age younger than 3 years, subtotal resection (i.e., more than 1.5 cm² residual), and leptomeningeal dissemination.²⁴ Patients without these risk factors are termed “average risk”; the presence of any one of these factors will place a patient in the “high-risk” category. When this stratification and treatment with risk-adjusted craniospinal irradiation with additional radiation to the primary tumor site and subsequent high-dose chemotherapy supported by stem cell rescue are used, the 5-year survival outcomes are 60% for high-risk patients and 75% for average-risk patients.

In general, patients should undergo maximal safe tumor resection, high-dose radiation to the tumor bed, some form of craniospinal radiation (\pm risk adjustment), and subsequent chemotherapy (\pm stem cell rescue).^{7–9,12,24–29} There are efforts under way to treat patients with resection and chemotherapy alone in order to delay, or altogether avoid, the potential costs of radiotherapy (RT), particularly in patients younger than 5 years of age.³⁰ Rates of 5-year event-free survival (EFS) and overall survival (OS) were 39% total for high- and low-risk patients (24% for high-risk patients, 53% for average-risk patients), and 49% total for high- and low-risk patients (33% for high-risk patients, 62% for average-risk patients), respectively. In this study, patients with nonpineal supratentorial PNET had a survival advantage over patients with pineal PNET. For patients with RT-naïve, chemoresponsive recurrences, myeloablative doses of thiotepa-based chemotherapy followed by stem cell rescue and RT may still offer the chance of cure.³¹

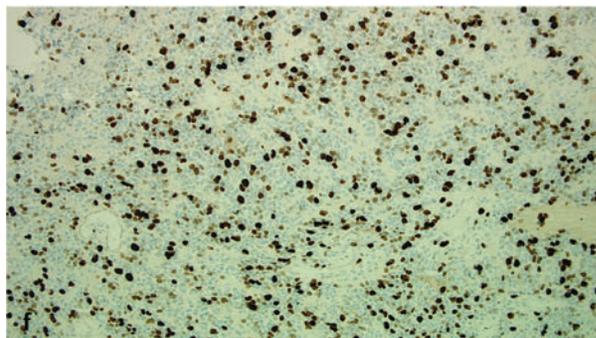
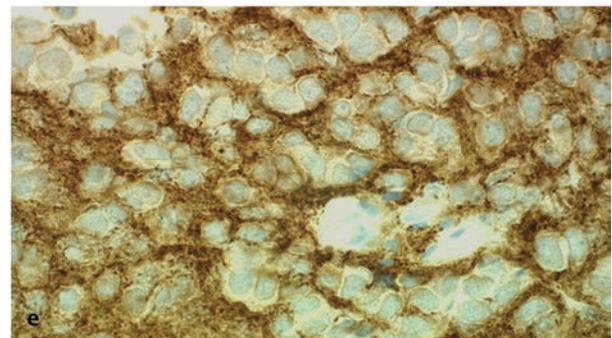
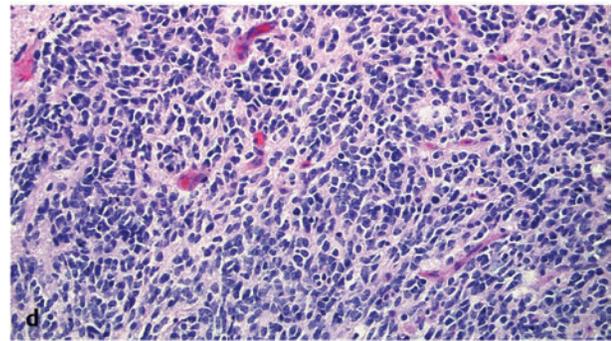
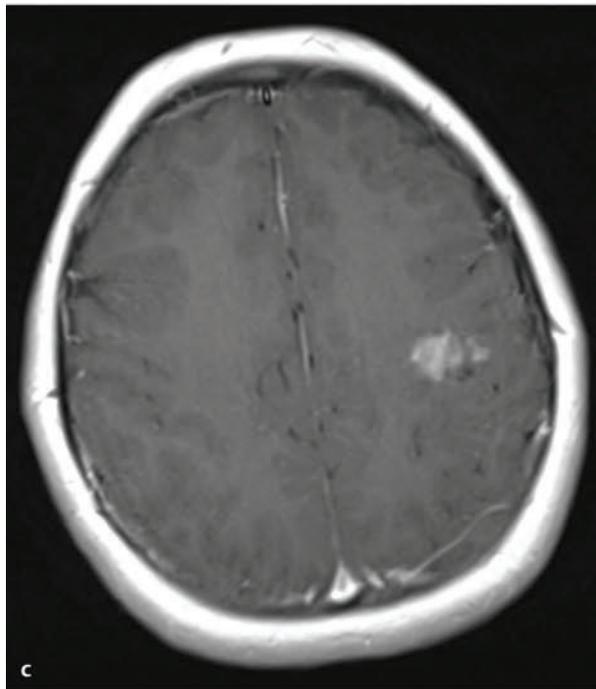
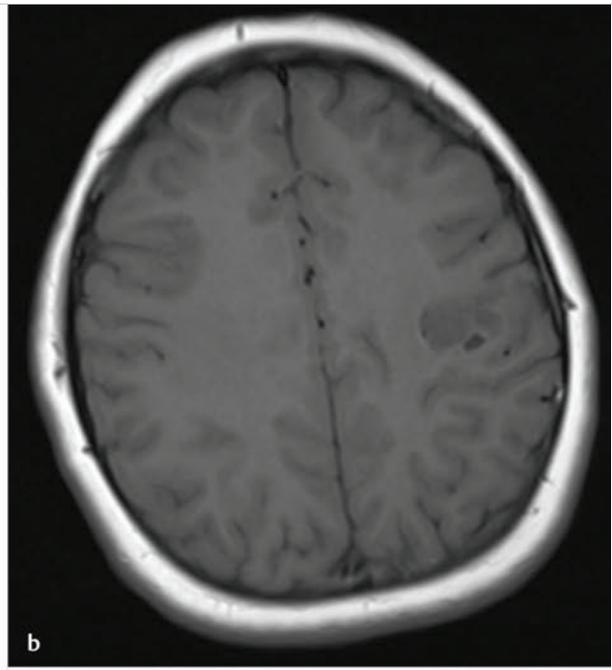
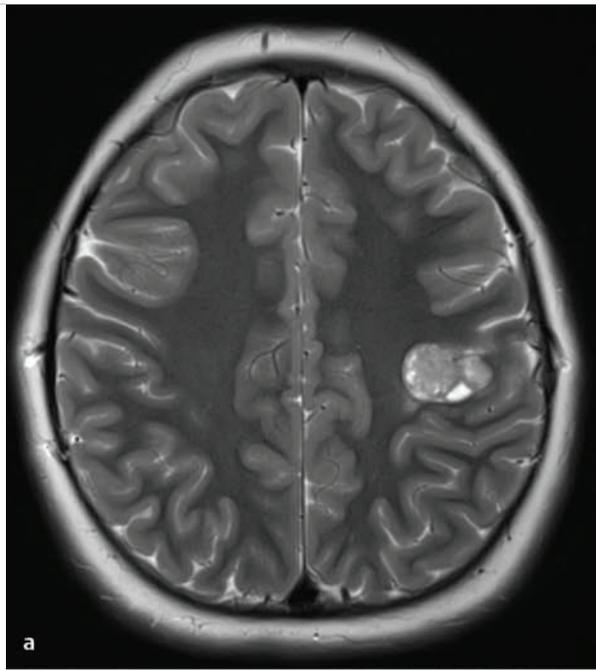


Fig. 35.1 (a) Axial T2 magnetic resonance (MR) imaging and T1 MR imaging (b) with and (c) without contrast of a typically appearing supratentorial primitive neuroectodermal tumor (PNET) in a 9-year-old girl with classic Jacksonian seizures. The tumor is hyperintense on T2 with associated cystic areas. Heterogeneous enhancement is present after gadolinium administration. (d) Supratentorial PNET is hypointense to isointense on T1 imaging without contrast. Hematoxylin and eosin stain (x20) (e) shows a patternless sheet of small cells with positive reactivity to synaptophysin antibodies, (f) indicative of neuronal differentiation and a high rate of cellular proliferation (antibody to Ki-67 protein).

35.2 Glioneuronal Tumors: Gangliogliomas/Gangliocytomas/Desmoplastic Infantile Gangliogliomas

The tumors in this group have subtle differences but are considered together under the term *ganglioglioma*; where significant differences exist, they are detailed. Gangliogliomas are mixed neuronal–glial tumors and account for 4 to 9% of childhood brain tumors; patients often present with seizures, and these tumors account for up to 40% of all tumors responsible for epilepsy.^{32–40} In 1926, the term *ganglioglioma* was coined by O. C. Perkins for tumors composed of dysplastic neurons and neoplastic glia.⁴¹ Although the majority are cystic, temporal tumors in other locations are reported.^{33,34,40,42–44} The World Health Organization (WHO) considers them grade I or II, although anaplasia, necrosis, or an MIB labeling index above 10% can result in an upgrade to anaplastic (III) or malignant (IV).⁴⁵

Desmoplastic infantile gangliogliomas (DIGs) are typically very large lesions arising in the hemispheres, generally in infants. They are often misdiagnosed as malignant astrocytomas or sarcoma-type tumors because of their cellular appearance and mitotic activity.^{46,47} They have a desmoplastic stroma, neoplastic astrocytes and neuronal cells, and may have a high mitotic or Ki-67 indices or areas of necrosis. Despite this more malignant picture, these tumors are WHO grade I.⁴⁸

35.2.1 Imaging and Preoperative Evaluation

The appearance of gangliogliomas on both CT and magnetic resonance (MR) imaging suggests a benign tumor. They are hypodense to brain on CT and show high signal intensity on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images. Enhancement is variable and patchy when present (► Fig. 35.2). The lesion will involve the cortex and underlying white matter and will often be adjacent to dysplastic cortex.⁴⁹ There is often little mass effect or edema. Confirming the relatively indolent and benign nature of the tumor, the inner table of the skull can show some bowing due to the long-term pressure applied by the tumor.^{17,19}

DIG is a tumor of infants that is often massive and located in the frontoparietal areas. The vast majority of the mass effect is the result of intratumoral cysts. On MR imaging, there is typically a solid superficial mass or plaque that is avidly enhancing, with septa originating from the solid tumor. Large portions of the tumor enhance after gadolinium administration, including the solid superficial mass, the walls of the intratumoral cysts, and the multiple septa.^{50,51}

Gangliogliomas are more commonly seen in children; however, they can present later in adulthood. Patients generally present with seizures, although the mass effect rarely causes symptoms. Epilepsy resulting from these lesions is often resistant to medications.³³ Complete resection should be the goal as it results in the best outcomes for seizure and tumor recurrence, but it may not be possible because of tumor adherence to critical neurovascular structures. Fortunately, patients who undergo subtotal resection can also see improvement in their

seizures.^{49,52} Patients with multiple types of seizures or an extended history of seizures are best managed by a multidisciplinary epilepsy service as lesionectomy alone may not be sufficient for seizure control. These patients may require a more extensive imaging work-up, video electroencephalography (EEG) recording from surface or subdural electrodes, or intraoperative electrocorticography (ECoG).

35.2.2 Treatment and Outcome—Tumor Control

In patients whose tumors are amenable to total resection, no further therapy is required, and the risk for tumor recurrence is quite low. Gangliogliomas—including the desmoplastic variant—are generally benign tumors that are essentially cured by total resection.^{40,46,49,52–55} This optimistic view is tempered by the fact that those tumors arising from or extending into midline structures are difficult to resect and are often of a higher grade.^{40,42,56} These children have a higher risk for recurrence, even with radiation therapy. Some authors feel that midline tumors are different pathologically from gangliogliomas that arise in the hemisphere, and that adjunctive therapy, usually radiation, should be administered.^{34,40,42,56–58} However, the numbers involved are small, and at this time, close neuroimaging follow-up is considered acceptable until progression occurs. Pathologic grade and totality of resection are the best prognosticators for tumor control. In a combined series of over 150 pediatric patients with all grades of ganglioglioma, 94% of the patients remained alive at the most recent follow-up, 95% of patients who presented with seizures remained alive, and all patients with intractable seizures remained alive.^{34,57–60} Of patients with midline tumors, 76% remained alive. Ninety-seven percent of patients who had a gross total resection (GTR) remained alive, versus 80% who had a subtotal resection (STR).⁵⁶ Another study, of 42 patients, reported a 56% survival with high-grade tumors and 90% survival with low-grade tumors.⁶¹ Luyken et al reported local control to be significantly improved by a temporal lobe location, lower grade, and GTR.⁴¹ Karremann et al specifically looked at children with anaplastic histology and found an 88% estimated 5-year survival and GTR to be the best predictors of survival.⁶²

A more recent meta-analysis regarding the role of RT, which included many of the above patients, divided patients into four groups: GTR, GTR + RT, STR, and STR + RT.⁵⁴ Children were combined with adults for a sample size of 402 patients (232 patients [58%] ages 0 to 19 years). They calculated 10-year local control and OS for each group: rates of local control were 89%, 90%, 52%, and 65%, respectively, and rates of OS were 95%, 95%, 62%, and 74%, respectively. When high-grade tumors were considered, only local control was significantly improved by adding adjuvant RT to STR. They concluded that there was no role for RT when GTR is achieved, and that RT improved local control of both high- and low-grade incompletely resected tumors and therefore should be considered. Liauw et al had similar findings in their study and noted that salvage RT may be less effective than up-front adjuvant therapy.⁵⁵

DIGs are generally benign and amenable to complete surgical resection; when that can be accomplished, no further

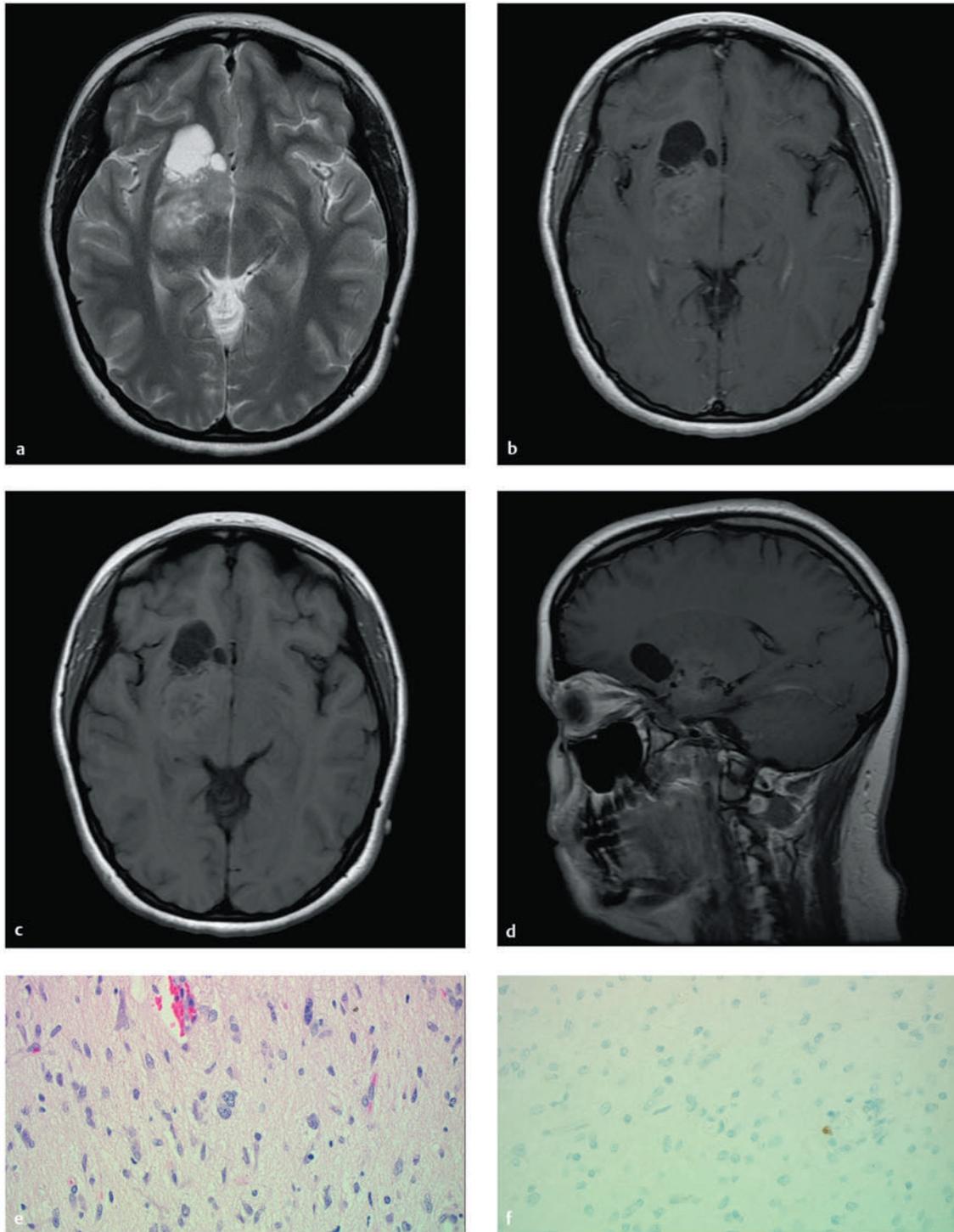


Fig. 35.2 Magnetic resonance imaging of a midline/basal ganglia ganglioglioma in a 17-year-old girl who presented with seizures. (a) Axial T2 image illustrates the typical solid/cystic nature of the tumor and hyperintensity. (b) Axial T1 images with and (c) without contrast demonstrate the enhancement pattern often found in this lesion. (d) The cystic, variably enhancing nature of this difficult tumor is demonstrated again in the sagittal plane with contrast. (e) Hematoxylin and eosin stain (x40) shows disorganized, pleomorphic neurons with binucleation and eosinophilic granular bodies and (f) virtually no cellular proliferation (Ki-67 stain).

therapy is warranted. If an STR is achieved or the tumor recurs, then either observation or re-resection is the appropriate course, respectively.^{50,51} Residual disease usually does not grow and can even spontaneously disappear.⁶³ Malignant

transformation has been reported necessitating chemotherapy.^{64,65} Radiation is typically not an option, given the very young age of the patients and the large treatment volume that would be required.

35.2.3 Treatment and Outcome—Seizure Control

Gangliogliomas are the most frequent cause of tumor-associated drug-resistant epilepsy in children.³³ Both the ganglioglioma itself and the often-associated surrounding cortical dysplasia—present in up to 80%—have been proved to be seizure generators.^{66–69} Patients whose epilepsy is not controlled with medications are excellent candidates for resective surgery. However, the question of whether lesionectomy alone can be performed or whether lesionectomy plus resection of surrounding tissue, including dysplastic cortex, is necessary to achieve optimal seizure control is unresolved. Some authors consider lesionectomy alone to be sufficient,^{36,38,49,52,70,71} whereas other authors suggest, when possible, resecting a margin of tissue around the ganglioglioma.^{35,41,57,67,72–74}

Giulioni et al performed lesionectomy alone on a mixed group of 15 glioneuronal tumors (73% gangliogliomas) and reported an 87% rate of seizure freedom (Engel class I).⁴⁹ They did not note an association with the type or duration of epilepsy, seizure frequency, or completeness of resection. Ogiwara et al took a similar approach in their group of 30 children with gangliogliomas.⁵² However, they used intraoperative ECoG in 21 patients and resected additional tissue if there was abnormal spike activity. When this was done, 11 of 21 patients had additional surrounding tissue removed. Ninety percent of their patients were seizure-free (Engel class I), and they noted no difference between the rates of seizure freedom in those who had ECoG and those who did not. Of note is that two of their three patients who continued to have seizures had lesionectomy alone performed on extratemporal tumors. Patients with extratemporal tumors treated with lesionectomy alone had 82% seizure freedom. In conclusion, regardless of the approach, most patients experience excellent outcomes with regard to their seizures. The use of ECoG and the extent of resection of tumor and surrounding tissue are decisions best made on a case-by-case basis.

35.3 Dysembryoplastic Neuroepithelial Tumors

DNETs were originally described by Dumas-Duport et al in 1988 and are almost universally associated with seizures.⁷⁵ Grossly, they have the appearance of an expanded cortex or a megagyrus; histologically, they show disorganized glial and neuronal elements that are characteristically arranged in a columnar appearance oriented perpendicular to the cortical surface. Cytologic atypia of neurons, a feature typical of gangliogliomas, is absent in DNETs. Foci of cortical dysplasia are found in 50 to 90% of cases.^{60,75–77} DNETs have a predilection for the frontal and temporal lobes and can also be multifocal, but the most common location is the temporal lobe. The presence of cortical dysplasia, young age at the onset of symptoms, and deformity of the overlying calvaria (in up to 60% of cases) suggest that this tumor has a dysembryoplastic origin. Dumas-Duport hypothesized that DNETs arise from the fetal subpial granular layer, an embryologic structure that involutes during the course of normal development.⁷⁸ It is currently accepted that surgery is the only required therapy, even if residual lesion is present or multiple resections are required.^{76,78–80}

35.3.1 Imaging and Preoperative Evaluation

DNETs characteristically appear as well-demarcated, hypodense, and nonenhancing lesions best seen on FLAIR or T2 sequences without peritumoral edema or mass effect (► Fig. 35.3).^{17,79,81} CT will demonstrate calcifications in about a quarter of all cases, and bony remodeling is common.⁷⁵ Almost all patients present with partial complex seizures, and as in patients with gangliogliomas, the seizures are often disabling because of their frequency, potential for secondary generalization, and poor responsiveness to pharmacotherapy.

35.3.2 Treatment and Outcome

The indications for surgery are either to obtain tissue for diagnosis or to control seizures. Most series of DNETs have been reported in terms of seizure outcomes. Engel class I outcomes are reported for 50 to 100% of patients.^{72,75,82–93} Some of these studies include several types of tumors and a mixture of pediatric and adult patients. For example, Chang et al reported a large series of 50 adult and pediatric DNETs with a mean follow-up of 5.6 years.⁸³ Over half of the cases were adjacent to areas of cortical dysplasia. Eighty-six percent of patients were seizure-free at 1 year (Engel I). Engel class I patients represented 80% of the group followed out to 10 years. Class I outcome was associated on multivariate analysis with complete resection and extratemporal location. For cases in which ECoG was used, the presence of extralesional spikes (and resection of that cortex) predicted better seizure control. This same group performed a meta-analysis of all reports of DNET and gangliogliomas in adults and children and found that, overall, 80% of patients were seizure-free after resection.⁹⁴ Short duration of epilepsy (less than 1 year), GTR, and focal seizure type predicted seizure freedom. Pathology (DNET vs. ganglioglioma), lesion location, age, and the use of ECoG were not predictive of seizure freedom. With respect to tumor control, residual tumor may remain dormant for many years, but there are reports of growth of histologically confirmed DNETs on neuroimaging that necessitated reoperation.^{75,95}

35.4 Choroid Plexus Papillomas/Carcinomas

CPPs and CPCs account for 2 to 6% of pediatric brain tumors and 10 to 20% of tumors in children younger than 1 year.^{96,97} The WHO classifies them as grade I (CPP), grade II (atypical CPP), and grade III (CPC).⁹⁸ Papillomas show a histologic architecture similar to that of normal choroid plexus; numerous papillae are covered with a simple columnar or cuboidal epithelium. Carcinomas exhibit brain invasion, nuclear atypia, an increased nuclear-to-cytoplasmic ratio, prominent and numerous mitotic figures, and a loss of the normal papillary architecture. The majority of tumors present with signs and symptoms of hydrocephalus because of their characteristically intraventricular location (most commonly in the atrium of the lateral ventricle) and propensity to overproduce CSF. They rarely present in brain parenchyma or the cerebellopontine angle.⁹⁹ Up to 30% of

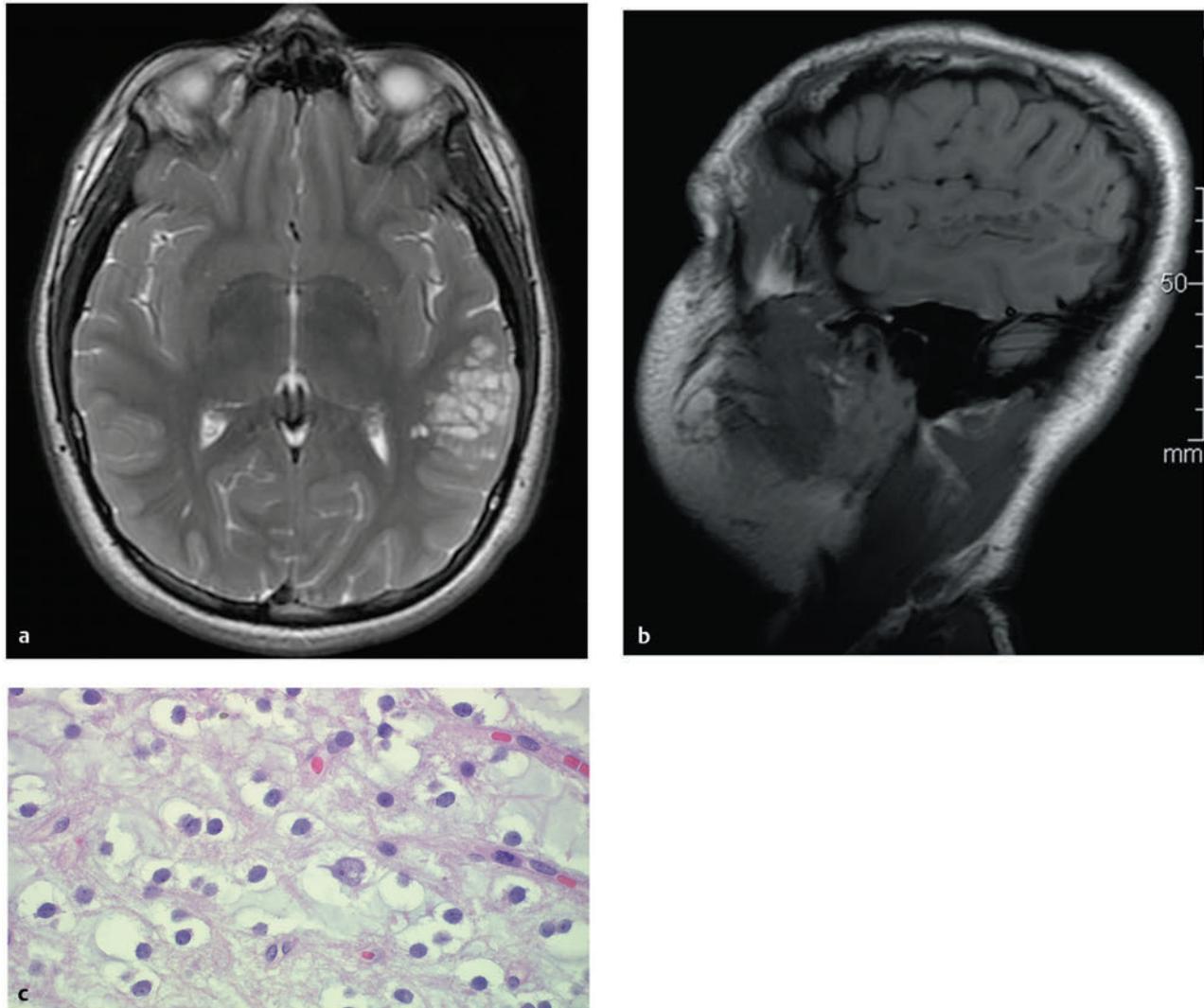


Fig. 35.3 This 13-year-old boy presented with seizures and a dysembryoplastic neuroepithelial tumor (DNET). (a) Axial T2 and (b) sagittal noncontrast T1 magnetic resonance images show the typical appearance of a “bubbly” expanded gyrus that is hyperintense on T2 and hypointense on T1. The lesion does not enhance. (c) “Floating neurons”—cortical ganglion cells sitting in small pools of mucin separated by cortical neuropil—are a common but nonspecific feature of DNETs (hematoxylin and eosin stain, x60).

patients with CPCs have metastatic disease at presentation, necessitating spinal screening for all patients.

35.4.1 Imaging and Preoperative Evaluation

Choroid plexus tumors are isodense to hyperdense to brain on CT and on MR imaging. They have a lobular, cauliflower-like appearance, can be quite large, are hypervascular, and generally enhance avidly with contrast. Hydrocephalus is present in 80% of patients with CPPs. Younger patients are more likely to have supratentorial tumors, whereas patients older than 14 years have a predominance of infratentorial tumors.⁹⁹ The presence of heterogeneity and surrounding edema of the brain raise the possibility that a lesion is a CPC (► Fig. 35.4).¹⁰⁰

35.4.2 Treatment and Outcome

Surgery is the primary treatment for choroid plexus tumors, but this can be challenging because of the hypervascular nature of the tumors coupled with the fact that they are usually found in young children who cannot tolerate excessive blood loss.^{101–105} This has led to preoperative measures to reduce the tumor’s blood supply. Atrial tumors typically have a dual supply from the posterior lateral and anterior choroidal arteries. Third ventricular tumors are supplied by the posterior medial choroidal artery. These arteries may be embolized immediately before surgery, or neoadjuvant chemotherapy, such as ifosfamide, carboplatin, and etoposide, may be administered—more commonly with CPCs—to devascularize the tumor.^{106–108} The neurosurgeon can tailor the surgical approach to coagulate the blood

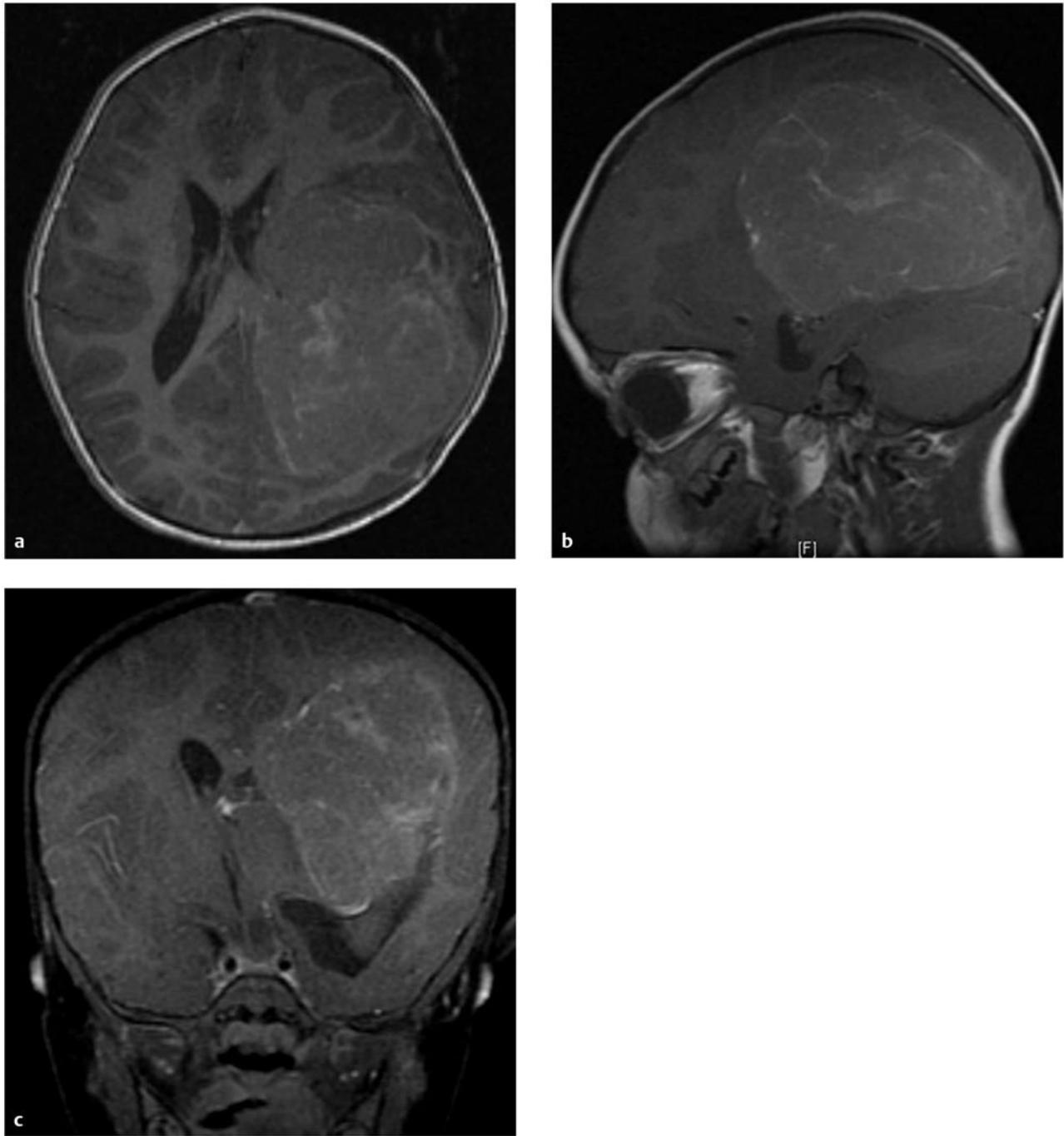


Fig. 35.4 Axial (a), sagittal (b), and coronal (c) gadolinium-enhanced T1 magnetic resonance images of a 4-year-old girl who presented with progressive hemiparesis. This choroid plexus carcinoma (CPC) was resected. The tumor is located within the ventricle, centered in the atrium, and has a variable enhancement pattern that is often suggestive of a CPC.

supply early, before resecting the tumor. If these feeding vessels are not accessible early in the case, then rapid tumor debulking is performed with the expectation that large volumes of blood products may need to be infused and the resection may require a “staged” approach. CPCs are more difficult to resect because they are friable, and a well-developed plane is lacking between the tumor and brain.

If a CPP is totally resected, then no further therapy is indicated.¹⁰⁹ The 5-year survival rate is close to or at 100% in many published series.¹¹⁰ A patient with a CPC who undergoes GTR, rather than STR, has a better chance at long-term survival, but even with GTR, the 5-year survival rate ranges from 30 to 50%. Most authors agree that a completely resected CPC requires adjuvant chemotherapy. For example, a meta-analysis by Wrede

et al found that postoperative chemotherapy resulted in a survival benefit, both with RT and without.¹¹¹ For the subgroup of patients with STRs, 2-year overall survival was better with chemotherapy than without (55% vs. 25%). The addition of RT predicted better survival (47.4% vs. 25.2%). Most authors suggest postoperative chemotherapy for younger patients (i.e., younger than 3 years) and combination chemotherapy and RT for older patients (i.e., older than 3 years).¹¹¹⁻¹¹⁵

CPC is often associated with Li-Fraumeni syndrome, in which patients have a germline mutation of *TP53*, a tumor suppressor gene located on the short arm of chromosome 17.¹¹⁶ This mutation is thought to confer resistance to both RT and chemotherapy.¹¹⁷ Some authors suggest Li-Fraumeni screening of all patients with CPCs.^{109,118} Patients with CPCs without germline *TP53* mutations had a 5-year survival of 82%, compared with 0% if they harbored a mutation.

35.5 Meningiomas

Meningiomas are rare in children, accounting for 1 to 2% of all meningiomas and 0.7 to 4.2% of pediatric brain tumors, but they are becoming more common with an increasing population of long-term survivors of brain tumors who have received cranial irradiation.¹¹⁹⁻¹²⁶ The presentation may include elevated intracranial pressure, the new onset of seizures, and focal neurologic deficit. Pediatric meningiomas are strongly associated with neurofibromatosis type 2 (NF-2) and to a lesser degree neurofibromatosis type 1 (NF-1).¹²⁷ Unlike meningiomas in adults, childhood meningiomas are more commonly seen in the posterior fossa, along the orbital nerve, in the ventricles, and without dural attachment in the brain parenchyma or within the sylvian fissure.¹²⁸ The WHO classifies meningiomas as grade I (typical), II (atypical), and III (anaplastic).^{119,120}

35.5.1 Imaging and Preoperative Evaluation

Pediatric meningiomas are similar to adult tumors with the exception that necrosis and cyst formation are more common in children. They are isodense to hyperdense to brain on CT, with calcification often present. MR imaging often shows an isodense mass that avidly enhances and generally has a dural attachment (► Fig. 35.5). Hyperostosis is present in approximately 50% of children with these tumors. Infantile meningiomas can be very large and are often associated with very large intratumoral cysts.^{17,129} As in choroid plexus tumors, preoperative angiography with embolization may be helpful in detailing the vascular anatomy and decreasing the blood supply in preparation for surgical resection. Conventional angiography or MR venography is also helpful in evaluating sinovenous patency for tumors that involve these structures.

35.5.2 Treatment and Outcome

Some authors feel that meningiomas are more aggressive in children than in adults, given the higher rates of recurrence even after GTR, which is likely the consequence of a higher rate of aggressive histopathology.^{127,130} A recent imaging study found no correlation of cystic components, MR characteristics,

peritumoral edema, or size with histopathologic grade.¹³¹ Because RT has a negative effect on the developing nervous system and radiation-induced tumors have a good outcome after complete resection, total removal of the tumor should be the goal, with focal radiation or stereotactic radiosurgery reserved for recurrences.¹³²⁻¹³⁴ Patients who develop radiation-induced meningiomas have excellent outcomes with single-modality therapy (i.e., surgery or RT), with a 5-year survival of 89%.¹³⁵

35.6 Miscellaneous: Central Neurocytomas, Germ Cell Tumors, and Others

Central neurocytoma is typically thought of as an intraventricular tumor, most commonly occurring in the supratentorial ventricles.¹³⁶ The first report of an extraventricular neurocytoma was in 1989, but this entity was not included in the WHO classification until the 2007 revision.^{137,138} Extraventricular neurocytomas have been described in the cerebellum, brainstem, skull base, and spinal cord but are usually large, well-circumscribed lesions located in the cerebral hemispheres, with a predilection for the frontal and parietal lobes.¹³⁹⁻¹⁴³ A number of pediatric case reports are found in the literature.¹⁴⁴⁻¹⁴⁷ Radiographically, these tumors are well demarcated and can be quite large with heterogeneous enhancement—often cystic and calcified—and they may or may not be associated with edema, hemorrhage, or necrosis.¹⁴⁸ Treatment is complete surgical resection. If this is not possible, then close radiographic follow-up is needed, with radiation reserved as an option for progressive disease or residual disease in older children.¹⁴⁹

Germ cell tumors are rarely hemispheric and therefore are discussed only briefly. They are seen primarily in children and are much more common in the Asian population. In the Caucasian population, 0.5 to 3% of pediatric tumors are of the germ cell type.^{150,151} The incidence is 11% in Taiwan and 5 to 15% in Japan. Most germ cell tumors arise in the pineal or suprasellar region, but they can be seen in the hemispheres or basal ganglia.¹⁵²⁻¹⁵⁷ CSF metastases occur in 3 to 37%; thus, all patients require neuraxis imaging and CSF cytology. Mature teratomas are best treated with surgery alone because they continue to grow and exert mass effect on adjacent structures. Germinomas are best treated with chemotherapy and/or radiation, with surgery reserved for diagnostic purposes when CSF fluid and serum markers (alpha fetoprotein and β -human chorionic gonadotropin) are ambiguous.¹⁵⁸⁻¹⁶³ Multiple studies suggest a cure rate of well over 90% with radiation therapy. Early results for chemotherapy alone in germinoma showed a significant recurrence rate.¹⁵⁹ However, the use of craniospinal radiation in germinoma without dissemination versus ventricular volume radiation is considered controversial, as is the need for chemotherapy after focal radiation alone.¹⁶⁰

Nongerminomatous germ cell tumors are rare. Tumor markers are elevated, and initial therapy is usually chemotherapy followed by resection for residual disease. With complete resection, no leptomeningeal or CSF spread, and aggressive radiation therapy, one should expect a 5-year PFS rate of 60%.^{153,154,161} The presence of metastatic disease is an ominous sign.

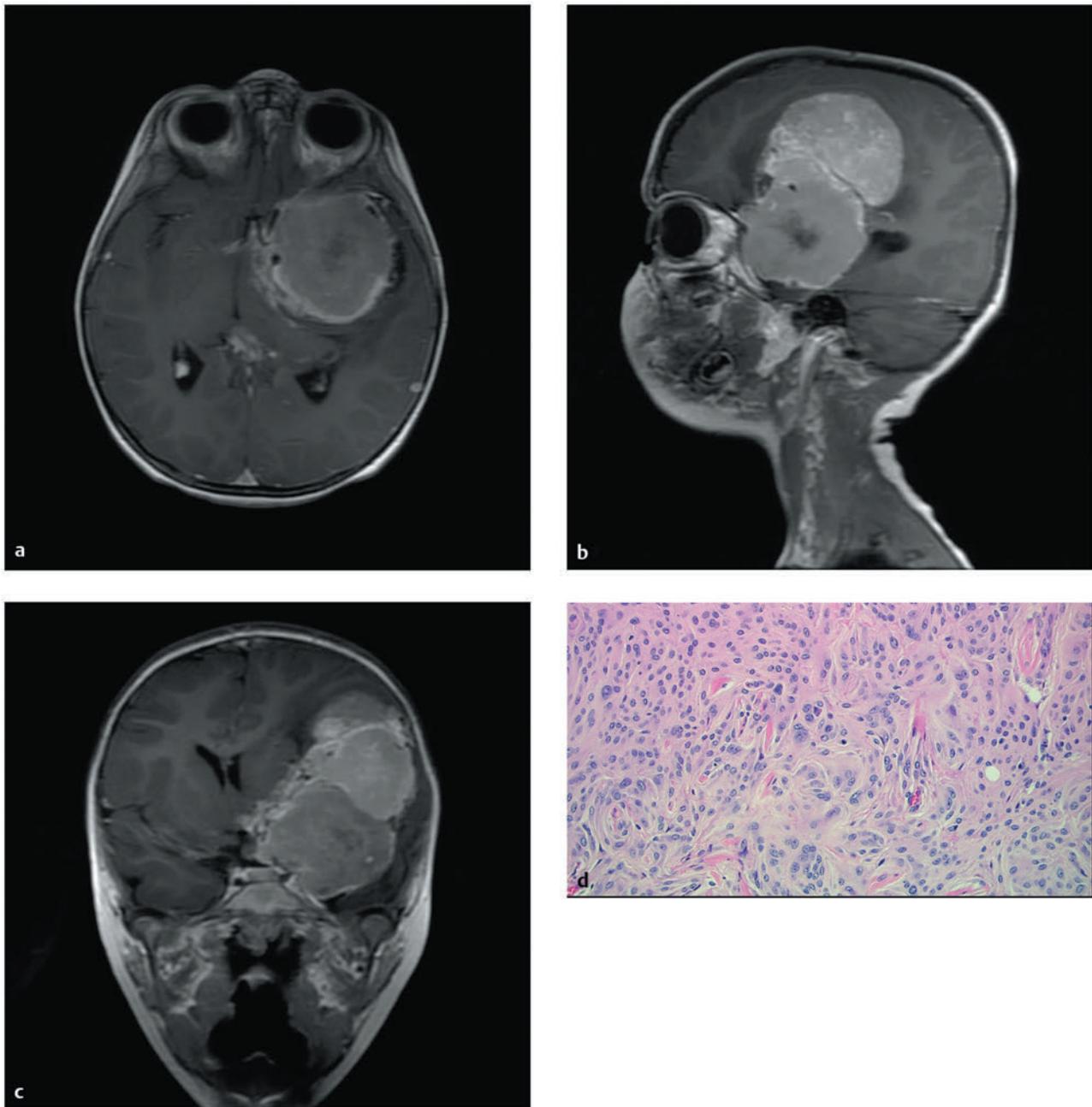


Fig. 35.5 (a) Axial, (b) sagittal, and (c) coronal gadolinium-enhanced T1 magnetic resonance images of a 22-month-old boy who presented with progressive hemiparesis. This large meningioma was resected. Imaging is similar to that of adult meningiomas. The tumor originated from the dura overlying the clinoid and sphenoid wing. (d) Meningothelomatous-type meningioma (hematoxylin and eosin stain, x20) is characterized by whorls, lobules, indistinct cell borders due to interdigitating cell membranes, and intranuclear pseudo-inclusions (pale areas of the nucleus due to cytoplasmic invaginations). There is a mitotic figure in the middle of the picture.

The remainder of the tumors seen in the cerebral hemispheres of children represent fewer than 5% of all pediatric brain tumors. Several benign tumors are cured with complete resection, including intraparenchymal schwannomas.^{162,163} Metastasis rarely occurs in children but has been reported in patients with sarcomas (e.g., Ewing sarcoma, osteogenic sarcoma), germ cell tumors, neuroblastoma, and Wilms

tumor.^{164,165} The adult experience suggests that resection of accessible lesions followed by adjunctive therapy prolongs survival. Primary central nervous system lymphomas are very rare in children, can be located within the cerebral hemispheres, and may be associated with prior cranial radiation, as some patients are long-term survivors of childhood leukemia.^{166,167}

Pearls

- These tumors are relatively rare, and thus, one should review the relevant literature before deciding on a treatment plan.
- With the exception of germinomas and nongerminomatous germ cell tumors, maximal cytoreductive surgery is the primary mode of treatment for these tumors.
- Like medulloblastomas, supratentorial PNETs require multimodal therapy, but they have a worse prognosis.
- DNETs and gangliogliomas should be resected in patients with medically intractable epilepsy. Areas of cortical dysplasia can be present within, or adjacent to, these tumors. Patients with long-standing seizures (i.e., longer than 1 year) may require a more extensive preoperative work-up of their seizures and intraoperative ECoG because resection beyond the actual lesion may be needed to control seizures.
- Although often massive at presentation, DIGs can usually be safely resected.
- Patients with gangliogliomas, DNETs, DIGs, and meningiomas rarely need adjuvant therapy—even when residual tumor is present—but do require long-term clinical and radiologic follow-up. Re-resection in patients with recurrent or progressive disease is usually the best therapy.
- The extent of resection is the most important prognostic factor for supratentorial PNETs and CPCs in patients presenting without metastatic disease. Residual tumor warrants a second resection.
- Measures to minimize blood loss during the resection of CPTs can be taken preoperatively (i.e., with embolization or neoadjuvant chemotherapy) and intraoperatively (by eliminating the main vascular pedicle).

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36 Optic Pathway Gliomas

Ben Shofty, Liat Ben-Sira, Anat Kesler, and Shlomi Constantini

Optic pathway gliomas (OPGs) are one of the most challenging neoplasms in modern pediatric neuro-oncology. Recent advances in imaging, surgery, and chemotherapy may lead to a better understanding of the pathophysiology and better clinical results. This chapter reviews these advances and the current treatment paradigms.

36.1 Definition and Classification

The term *optic pathway glioma* is used to define low-grade glial neoplasms that are epicentered within the visual system: the optic nerve (ON), optic chiasm, optic tracts, and, rarely, the optic radiations. The various presentations of OPG are illustrated in ► Fig. 36.1. These lesions tend to have an erratic natural history, and they require careful follow-up and management by a multidisciplinary team. The subset of patients seen by pediatric

neurosurgeons may be biased toward the aggressive end of the spectrum, with tumors that have a tendency to progress and require multiple treatment lines.

OPGs comprise a wide spectrum of anatomical variations. In addition, age, the coexistence of neurofibromatosis type 1 (NF-1), histology, and molecular markers may be important factors in the clinical behavior of OPGs and in the practical process of individualized decision making regarding their treatment.

Several different methods have been developed for the classification of OPGs. Dodge et al introduced the first of these in 1958.¹ The Dodge system classifies OPGs into three groups based on the anatomical location of the tumor (► Fig. 36.2). Tumors of the ON are Dodge I, tumors of the chiasm are Dodge II, and posterior tumors, or those that extend into nearby structures, are Dodge III. This method, defined in the era before computed tomography (CT) and magnetic resonance (MR)

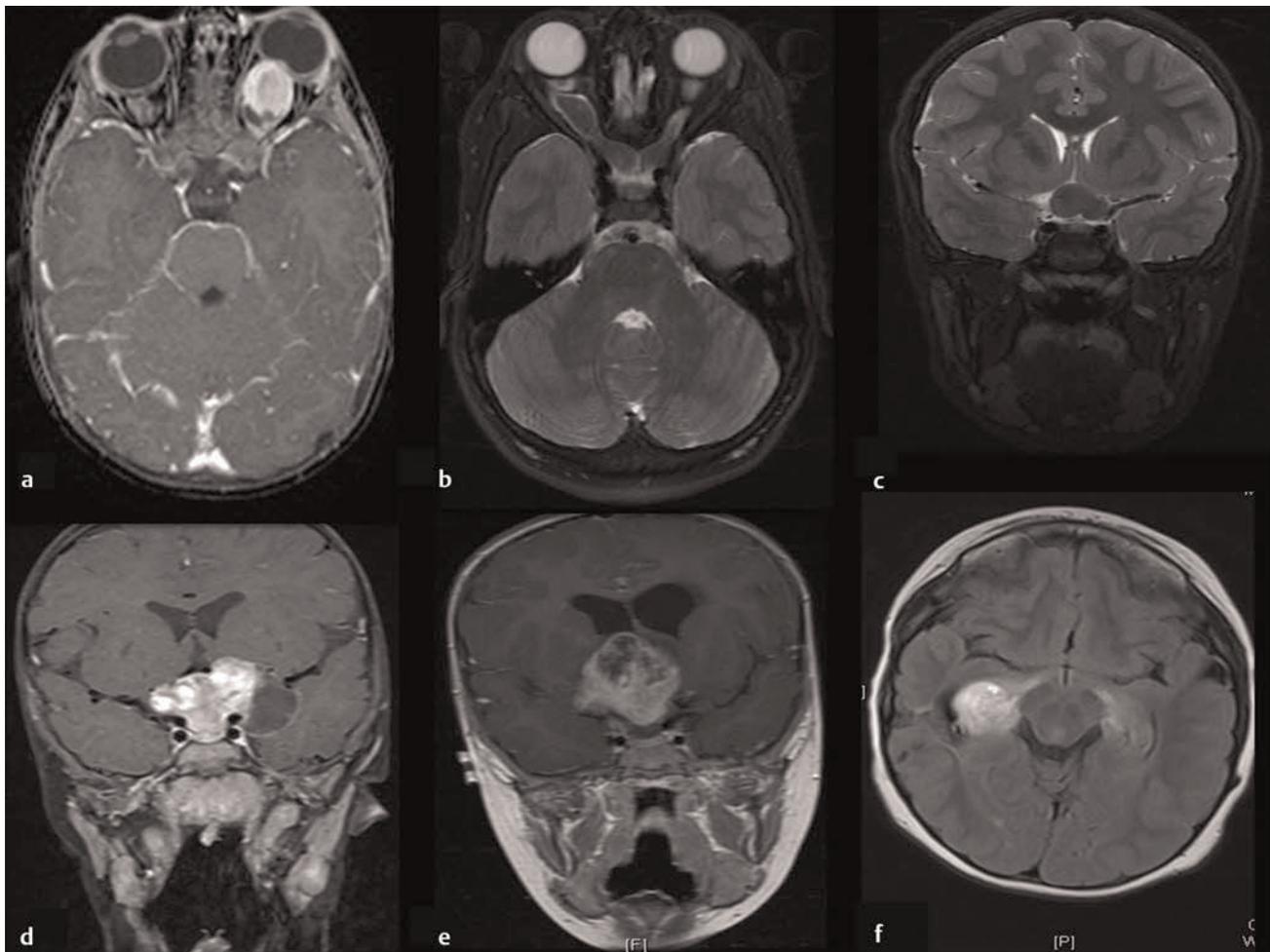


Fig. 36.1 Various presentations of optic pathway glioma. (a) Isolated optic nerve (ON) glioma of the left ON. (b) Bilateral ON glioma involving the chiasm. (c) Chiasmal glioma with no involvement of the hypothalamus. (d) Large chiasmal glioma involving the hypothalamus with a cystic component. (e) Large chiasmatic/hypothalamic glioma that compresses the third ventricle, causing hydrocephalus. (f) Posterior glioma of the optic radiations.

imaging, is still widely used, mainly for research purposes. However, its clinical relevance is limited.

The *modified Dodge* classification system, developed in 2008,² is a more detailed anatomical classification that breaks down each component into several highly precise categories. The modified Dodge system also takes into account additional factors, such as the existence of NF or leptomeningeal dissemination.² This method, although very precise anatomically, is probably too complicated to be routinely implemented in clinical patient care. Another drawback of both Dodge classification methods is the lack of sensitivity to indicate tumor progression.

A third classification system that attempted to address the issue of functional status was suggested by McCullough and Epstein in 1985.³ This classification system consists of two components, tumor/anatomical and functional. The *tumor component* is divided into four classes (T1, one ON; T2, both ONs; T3, optic chiasm; T4, hypothalamus/thalamus). The *functional component* is divided into five classes (V0, normal; V1, impaired, one eye; V2, impaired, both eyes or blind, one eye; V3, blind, one eye and impaired, one eye or field defect; V4, blind, both eyes). We recently suggested a new morphological classification that utilizes recent advances in imaging and may aid in clinical management and patient stratification (► Table 36.1, ► Fig. 36.3).

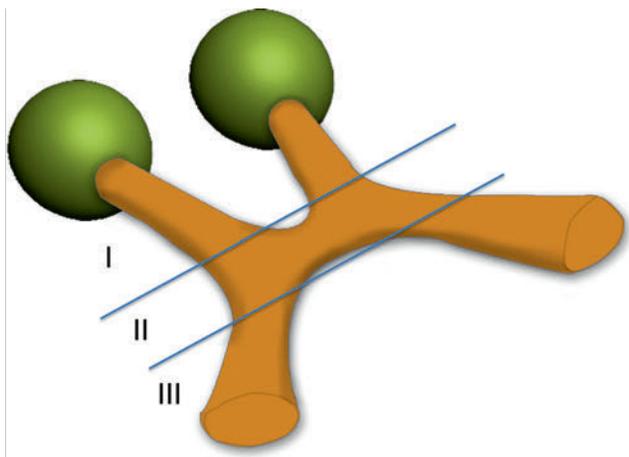


Fig. 36.2 Schematic representation of the 1958 Dodge classification system. I, optic nerve glioma; II, chiasmatic glioma; III, posterior glioma or chiasmatic with involvement of extraoptic structures.

Other factors that should be considered in an attempt to stage an OPG are the presence of NF-1, the age at diagnosis, the symptoms at presentation, and the risk for hydrocephalus.

Caution is warranted when attempts are made to classify OPGs in patients with NF-1. Despite the fact that this is a relatively common tumor in patients with NF-1, many radiologic abnormalities may complicate the diagnosis. An example of such misleading abnormalities are T2 hyperintensities that sometimes have mass effect, and focal signal changes within the ON that may be either preneoplastic or without any significance.

36.2 Epidemiology

OPGs are the most common primary neoplasms of the neural visual pathways, comprising approximately 1% of all central nervous system (CNS) neoplasms in the general population and approximately 5% of CNS neoplasms in children.⁴ The annual incidence (as reported in the pre-MR imaging era) is 1 per 100,000.⁵ The real number is probably higher. Of all patients with this diagnosis, 80% are in the first decade of life, and 90% are in the first two decades. The mean age at diagnosis is 8.8 years in older series and ranges between 2.7 and 5.4 years in more recent series.⁶⁻⁸ An estimated 37% of OPGs tend to progress.⁹ There is no gender predisposition. In a large series published by Nicolin et al, 58% of 133 patients with OPG were positive for NF-1. The mean age at diagnosis in this series was 5.9 years, 50% of the tumors were hypothalamic/chiasmatic, 60% were diagnosed by imaging only, and 52% required treatment over the course of a follow-up period of 9 years.¹⁰ The high proportion of Dodge II or III tumors in this series may be attributable to a referral bias.

36.3 Optic Pathway Glioma and Neurofibromatosis Type 1

OPGs are one of the diagnostic criteria for NF-1, and bilateral OPGs are considered pathognomonic for NF-1. With regard to outcome, the simultaneous occurrence of the two diseases is considered a good prognostic factor.^{9,11} In a series comparing OPGs associated with NF-1 and sporadic gliomas, the children with NF-1 had a significantly better clinical picture at diagnosis, with less increase in intracranial pressure, less decrease in visual acuity, and fewer abnormalities of the fundus of the eye.

Table 36.1 Morphological classification of optic pathway glioma

Nerve	Chiasm	Posterior	General
1. Mild thickening	1. Confined to chiasm	1. Focal involvement	Cyst: yes/no
2. Severe thickening	2. Chiasm and hypothalamus	2. Extensive involvement	Hydrocephalus: yes/no
Enlarged ONSD: yes/no	3. Chiasm and third ventricle		Other CNS malignancies: yes/no
Tortuous ON: yes/no	4. Major suprasellar involvement		Diffuse NF-related changes: yes/no
Pressure on globe: yes/no			Age at presentation?
Enhancement: yes/no	Enhancement: yes/no	Enhancement: yes/no	Favorable molecular properties?
Isolated involvement: yes/no	Isolated involvement: yes/no	Isolated involvement: yes/no	

Abbreviations: CNS, central nervous system; ONSD, optic nerve sheath diameter; NF, neurofibromatosis.

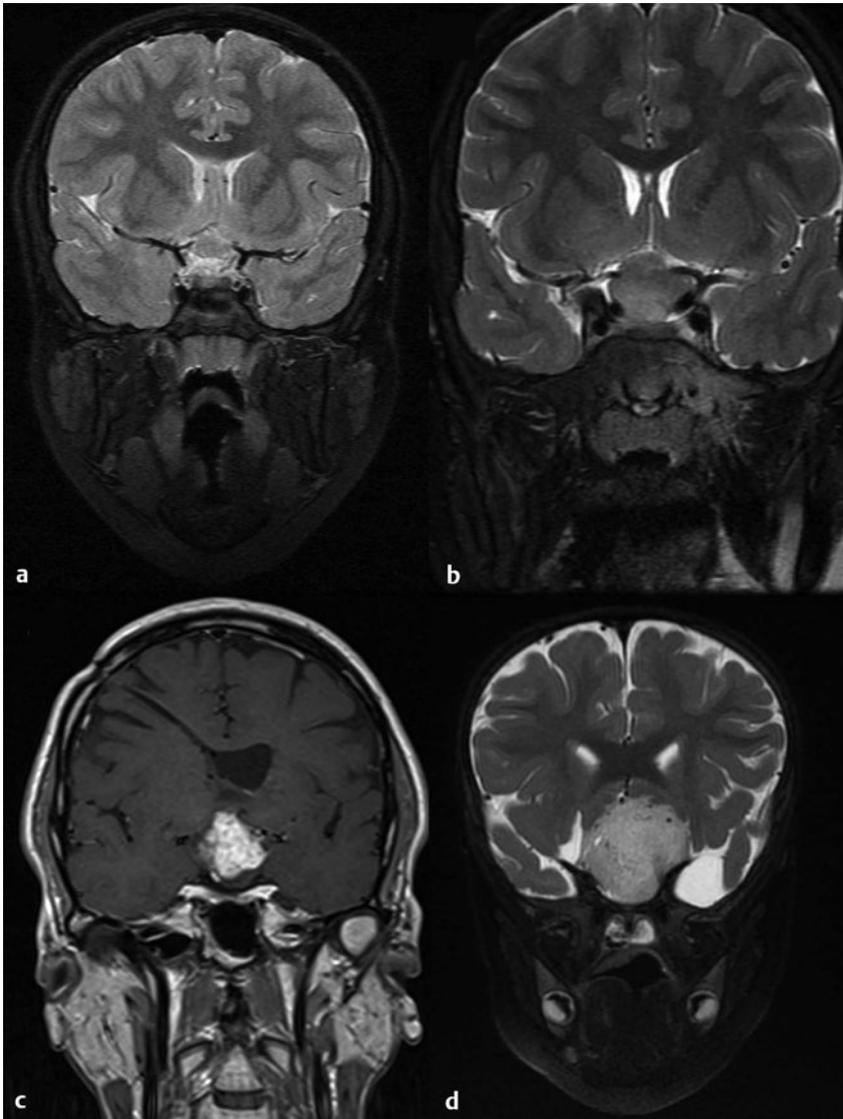


Fig. 36.3 Four different classes of chiasmatic/hypothalamic glioma. (a) Chiasmatic thickening only. (b) Chiasm and hypothalamus. (c) Chiasm and third ventricle involvement. (d) Major supra-sellar involvement.

Radiologic progression, visual deterioration, and endocrine damage were also less frequent in children with OPGs associated with NF-1.

OPGs appear in almost 30% of patients with NF-1 and may present with a variety of radiologic and clinical changes.¹² In patients with NF-1, the lesion is more likely to be located anteriorly and involve a single nerve than in patients with generic OPG.¹³ The spectrum of imaging appearances in patients with NF-1 is broad, ranging from fine signal changes on T2-weighted MR images, to an enlarged ON sheath, to gross ON tumors and chiasmatic lesions that protrude into the third ventricle or other neighboring structures. When posterior tumors are being considered in patients with NF-1, it is important to remember that they may easily be confused with NF-related T2 hyperintensities that may be expansile and have a mass effect. A careful radiologic and clinical follow-up is warranted before any therapeutic decisions are made for lesions of the optic radiations. Historically, NF-1 OPGs were considered to be relatively indolent tumors that did not tend to progress. Recently, several

publications have described a more active clinical course, with progression of the tumor noted in up to 75% of patients with NF-1, even in children older than 11 years.¹⁴ Recently, macrocephaly has also been correlated with OPG in patients with NF-1.¹⁵

36.4 Clinical Presentation

Visual complaints such as decreased visual acuity, nystagmus, and proptosis are found at presentation in 46% of patients. Neurologic problems such as headaches, vomiting, and seizures are present in 16% of patients.¹⁰ These low percentages are attributed to the young patient age and the high percentage of patients whose tumors are diagnosed during routine screenings, especially patients with NF-1. The age at diagnosis of patients with generic OPGs is older than that of patients with NF-1. This is mainly attributed to the fact that a diagnosis is made only after clinical symptoms appear, not during routine screening, as in patients with NF-1.⁸

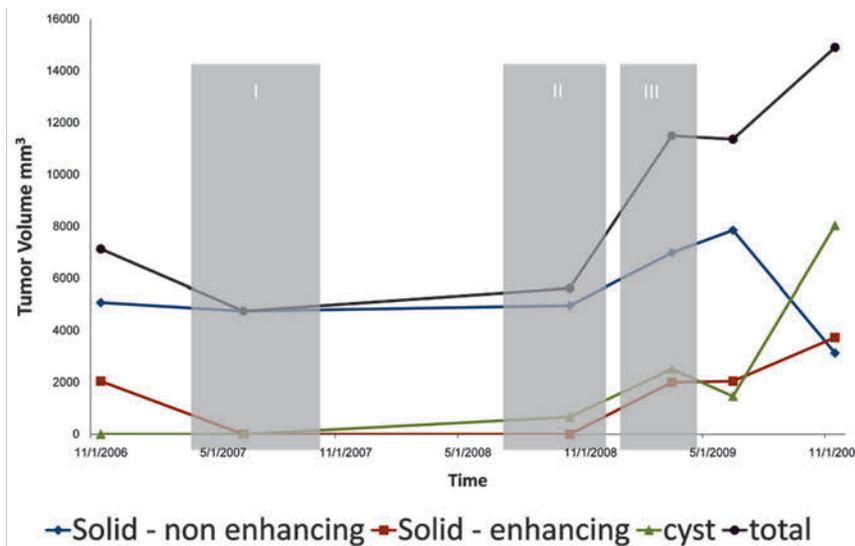


Fig. 36.4 Volumetric follow-up of one of our patients with internal segmentation into three components and integrated treatment periods. Note that despite the fact that the gross total tumor volume enlarges, there is a marked reduction of the solid component following chemotherapy. The main progression is of the cystic component. Total, gross total volume of the tumor; Solid-enhancing, volume of the enhancement-receiving bulk on magnetic resonance (MR) imaging; Solid-nonenhancing, volume of the solid portion of the tumor that does not receive contrast enhancement on MR imaging; Cyst, volume of the cystic component on MR imaging. I, treatment period with vincristine and carboplatin; II, treatment period with vinblastine; III, treatment period with rapamycin and erlotinib (Tarceva; Genentech, South San Francisco, CA).

The mode of presentation varies with the anatomical location of the tumor. Posterior tumors are associated with evidence of endocrine dysfunction, such as precocious puberty, and with hydrocephalus. Anterior tumors are associated more with visual abnormalities.¹⁶ Visual signs such as palsies of cranial nerves III, IV, and VI, papilledema, and optic atrophy are present in a minority of cases. The type of visual deficit usually correlates with the tumor location; posterior tumors may cause hemianopia, whereas unilateral ON tumors will cause monocular visual impairment. Signs and symptoms of raised intracranial pressure should be taken seriously because acute hydrocephalus has been reported as a presenting symptom. Diencephalic syndrome (cachexia, macrocephaly, nystagmus, and visual deficit) is seen in 21% of infants with chiasmatic/hypothalamic tumors.¹⁷

36.5 Diagnostic Studies

36.5.1 Radiology

MR imaging is the gold standard for the diagnosis of OPG. To maximize the diagnostic yield, MR protocols should be planned with the assistance of an experienced neuroradiologist and should include orbit-directed scanning with fat suppression and contrast injection. Tractography may prove beneficial in the future but so far remains experimental.¹⁸

Tumors may differ in MR appearance depending on their location, but they are usually isointense on T1 and hyperintense on T2, receive variable enhancement, and have cystic as well as solid nonenhancing components. Tumors of the ON usually do not have cystic changes, appearing as gross thickening of the nerve itself, with or without nerve sheath enlargement. The differential diagnosis for ON enlargement is broad and includes meningioma, neuroma, hemangioblastoma, and lymphoma.¹⁹ ON sheath enlargement is found in nonneoplastic conditions such as increased intracranial pressure, optic neuritis, Graves disease, sarcoidosis, toxoplasmosis, central vein occlusion, idiopathic intracranial hypertension, and tuberculosis.^{20,21} Posterior tumors may appear as minimal chiasm thickening, or as large

masses protruding into the third ventricle with apparent mass effect. Cystic changes are common and are a part of the natural history of the tumor. Neoplastic changes posterior to the lateral geniculate nucleus are rare and are difficult to differentiate from NF-1 T2 hyperintensities. Unfortunately, the initial radiologic appearance does not correlate with the visual prognosis. We have found deteriorating vision in patients with tumors that seem to be stable anatomically, as well as stable vision in patients whose tumors demonstrated structural progression. It has been suggested that dynamic contrast enhancement may correlate with progression, with larger mean permeability values in aggressive tumors.²²

Because of the long follow-up required in these patients and the importance of the early detection of changes in the tumor bulk or in its internal components, we recommend the use of volumetric assessments. These measurements, although time-consuming, may improve patient care by enabling more accurate decision making.^{23,24} ▶ Fig. 36.4 demonstrates a volumetric follow-up of one of our patients; the corresponding MR images are presented in ▶ Fig. 36.5.

36.5.2 Ophthalmology

Neuro-ophthalmology examination is crucial for both the diagnosis and follow-up of OPG, as visual decline is a worrisome consequence of the tumor. The neuro-ophthalmologic evaluation is often difficult, especially in young patients whose cooperation is limited. A decline in visual acuity is often present at diagnosis and sometimes may be the reason for initial testing, even in the very young (e.g., an infant who starts bumping into objects or sitting closer to the television). In addition, color vision, visual field, eye movements, relative afferent pupillary defect, pupil size, and the fundus should all be evaluated. Any progressive change should be considered seriously as a reason to initiate therapy. In very young children, a normal examination does not rule out visual impairment from an OPG. Recently, the use of optical coherence tomography (OCT) was shown to detect loss of the retinal nerve fiber layer in children with OPG (▶ Fig. 36.6). This may prove to be an auxiliary

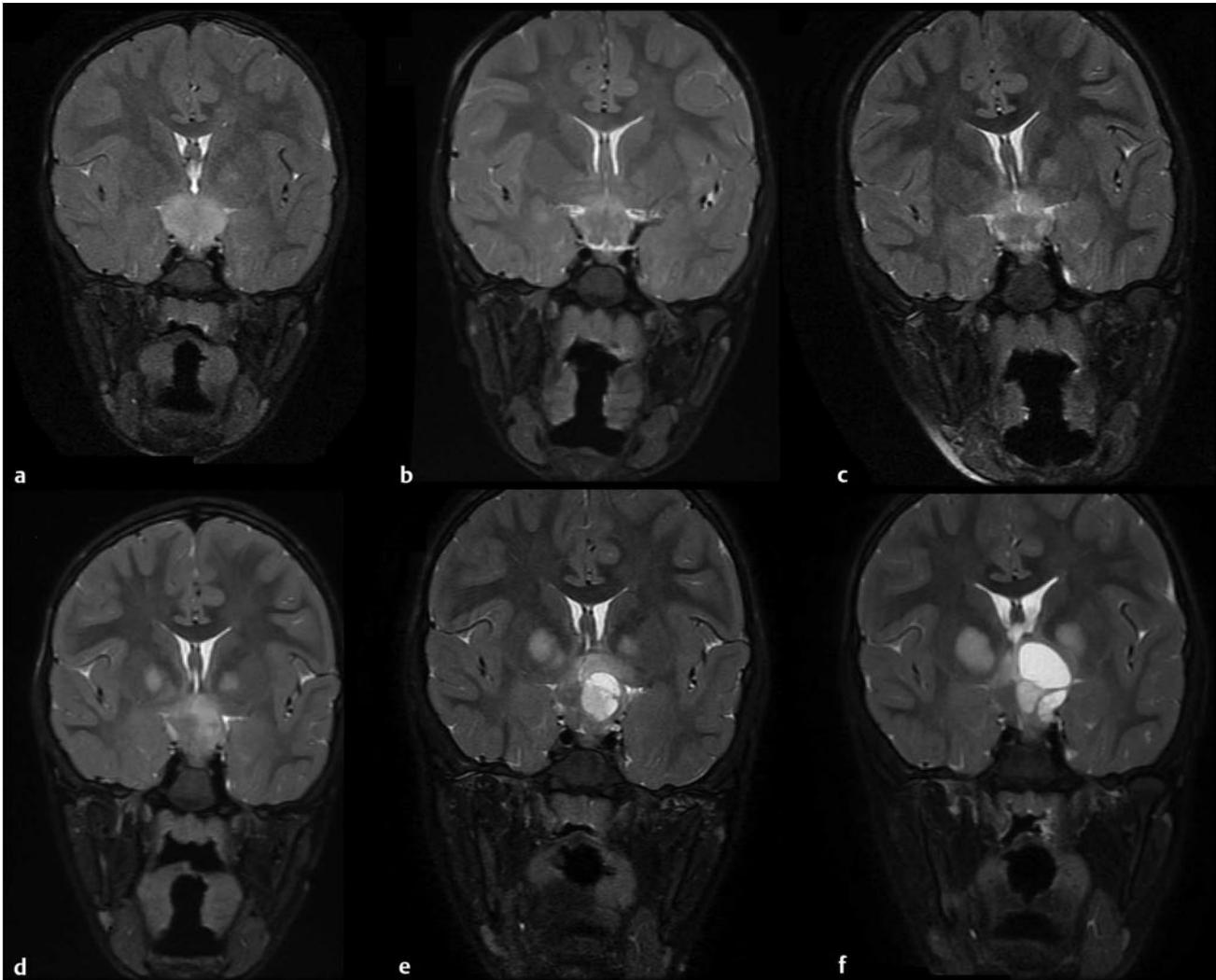


Fig. 36.5 Anatomical history of a chiasmatic/hypothalamic glioma. (a-f) Serial coronal T2 images of a 4-year-old boy with neurofibromatosis type 1 who presented with visual deterioration. Within 4 years, a deterioration to bilateral blindness occurred despite three different chemotherapy treatment lines. (e,f) Note the cystic changes that the tumor undergoes.

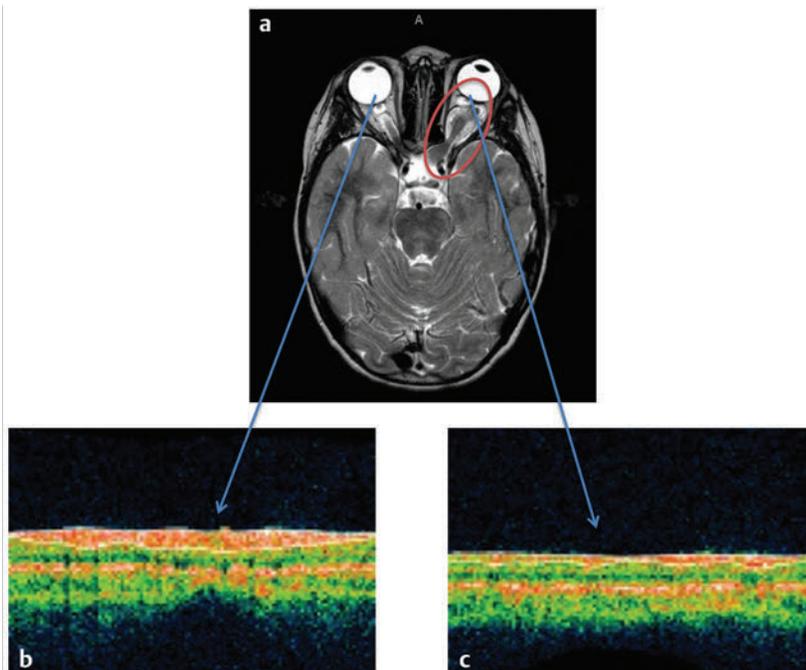


Fig. 36.6 Patient with neurofibromatosis type 1 and optic pathway glioma (a) with a tumor on the left optic nerve (red circle). Optical coherence tomography of the right, normal eye (b) and of the left, tumor-affected eye (c) (blue arrows). This patient had a visual acuity of 20/20 in the unaffected (right) eye and of 20/400 in the tumor-affected eye. Visual acuity correlated well with retinal nerve fiber layer thickness of 105 μm on the right (normal) versus 48 μm on the left (severely thinned). (Images courtesy of Dr. Robert Avery, Children's National Hospital, Washington, DC.)

tool in diagnosing visual damage in young children, as well as in providing evidence regarding visual reserve and the need for treatment.^{25,26}

36.5.3 Endocrine Assessment

An endocrine assessment should be done in any child with chiasmatic/hypothalamic glioma. Endocrine abnormalities such as central precocious puberty and growth hormone deficiency are detected in approximately 20% of patients with an OPG. It should be noted that growth hormone deficiency is present in approximately 2.5% of patients with NF-1, even those without OPG.²⁷

36.6 Pathology

OPGs are typically low-grade glial neoplasms. Pilocytic astrocytoma accounts for the vast majority of these tumors. The rest usually consist of fibrillary and pilomyxoid astrocytomas, oligodendrogliomas, and gangliogliomas. A more aggressive behavior pattern may be predicted with labeling indices such as high Ki-67^{4,28} as well as pilomyxoid histology.^{29,30} Malignant transformation is rarely seen and is most frequently associated with irradiation.³¹

36.7 Natural History and Prognosis

OPGs have an erratic natural history. Some of these tumors progress, others are steady for a lifetime, and others spontaneously regress.^{32,33} This has led to the theory that OPGs are not a single entity, but rather a group composed of two or even three subtypes that are often hard to distinguish from one another. These subtypes vary widely in their clinical and radiologic outcomes. Although some OPGs undergo spontaneous regression, a significant group of large chiasmatic/hypothalamic tumors tend to progress and even metastasize. ▶ Fig. 36.4 demonstrates a progressive OPG of the chiasmatic/hypothalamic type over 4 years of follow-up. Interestingly, of the 5% of low-grade gliomas that undergo leptomeningeal spread, OPGs account for approximately 50%.³⁴ Before this behavior pattern was recognized, these tumors were sometimes considered benign, even hamartomatous in nature,³⁵ requiring only careful follow-up; however, they are now perceived as progression-prone, persistent tumors that pose a major therapeutic dilemma. As many as 35% require treatment at presentation.¹⁰

Patients who do not require treatment at initial presentation have varying chances for progression. In those with NF-1, the likelihood of progression is 15%, whereas in patients with sporadic OPGs, the probability of progression is 75%.

Molecular analysis of tumor tissue has shown promising early results in predicting the course of the disease. In particular, the BRAF-KIAA 1549 fusion protein seems to indicate tumors with a tendency to arrested growth and even to spontaneous senescence. In a recent study, the 5-year progression-free survival (PFS) rate was 61% ± 8% for B-K fusion protein–positive patients and 18% for B-K fusion protein–negative patients. In this study, 61% of sporadic OPGs were positive for fusion

protein, and no OPG related to NF-1 was positive for this mutation.³⁶ Although not currently utilized in routine clinical practice, we believe that this analysis should be considered for any patient without NF-1 for whom therapeutic decisions are being made based on radiologic progression only.

36.8 Treatment

The follow-up and management of OPG require an experienced multidisciplinary team that provides individualized patient care. Only then can adequate therapeutic decisions be made. The goal of treatment is to prevent visual decline and to achieve long-term tumor control. In the presence of a severe mass effect or hydrocephalus, immediate, life-saving neurosurgical procedures may be indicated. In most cases, however, OPGs are not life-threatening tumors. The risk-to-benefit ratio of treatment must therefore be considered carefully for each patient.

The exact timing of treatment initiation is one of the major open questions in OPG management. In most cases, we recommend delaying treatment for as long as possible unless a clear radiologic progression or visual decline is noted. Treating an asymptomatic or minimally symptomatic stable patient seems to offer no advantage over observation alone.^{6,28,37} Thus, current guidelines suggest intervention *only* when there is a documented decline in vision or radiologic progression.⁹ Treatment initiation dilemmas may be very relevant in a child, especially an infant, who presents for the first time with compromised vision. At this moment, progression cannot be defined; however, compromised reserve may be a relevant reason to start treatment earlier rather than later.

We recommend imaging and neuro-ophthalmologic examinations (including visual field and OCT if available) every 6 months. Patients with compromised reserve for whom a decision has been made not to treat should be clinically examined more frequently. If the tumor is chiasmatic/hypothalamic, a detailed endocrinologic evaluation should be performed. If the patient has been stable for a period of a year and has no adverse prognostic factors, follow-up visits may be scheduled on a yearly basis.

The choice between treatment options such as surgery, chemotherapy, and irradiation is not easy and depends on the team's experience and biases. The following sections outline general rules for these treatment modalities. ▶ Fig. 36.7 illustrates a suggested management algorithm for OPG.

36.8.1 Biopsy

For tumors with a characteristic MR imaging appearance that are epicentered on the optic pathway, especially in a patient with NF-1, no biopsy is required.³⁸ Biopsies are indicated if the tumor has an atypical appearance on MR imaging, if the age of the patient is unusual (older than 10 years or younger than 1 year), or if the patient has unusual clinical characteristics (rapidly progressing or severe neurologic deficits other than vision loss). It has been argued that the mere knowledge that an OPG has pilomyxoid characteristics is important for early treatment decisions. The value of biopsy of an OPG for molecular diagnosis is still controversial. The example of the *BRAF* mutation, provided previously, may represent only the beginning of a

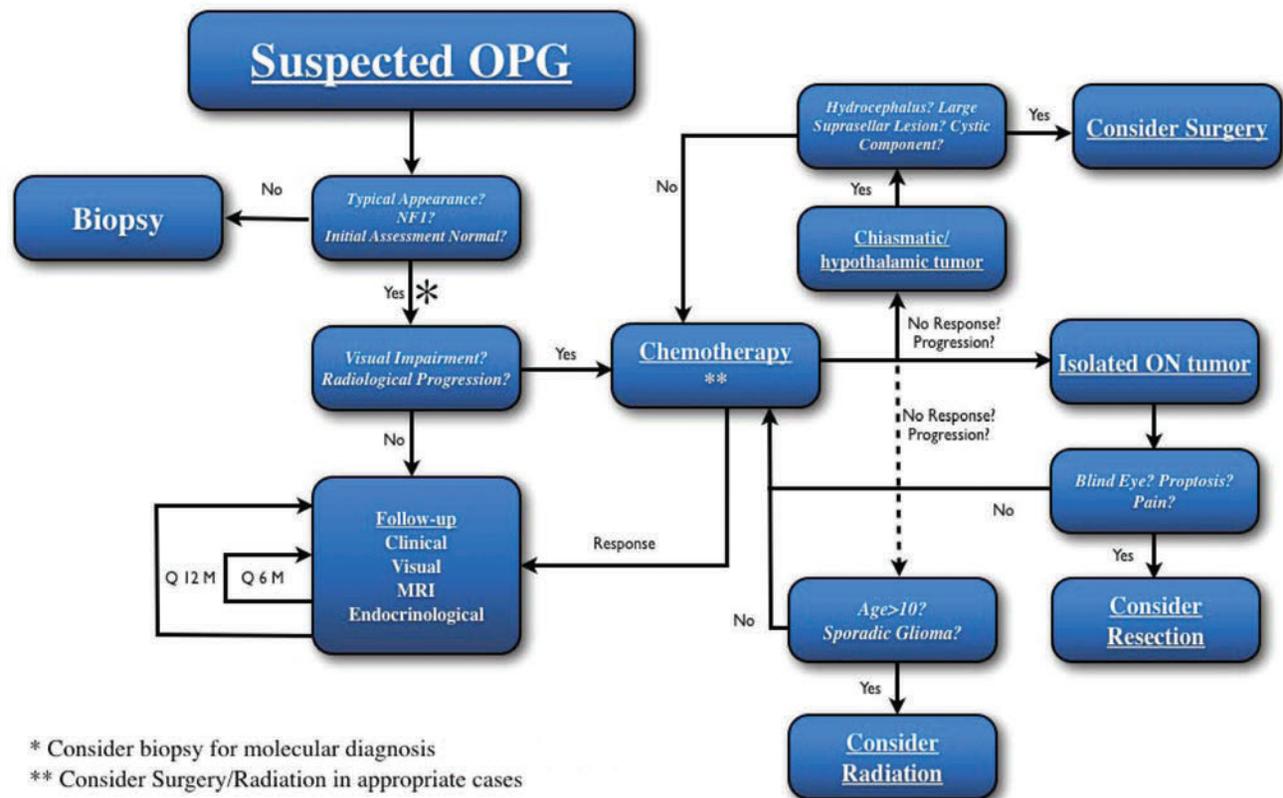


Fig. 36.7 Management algorithm for patients with optic pathway glioma. MRI, magnetic resonance imaging; ON, optic nerve; OPG, optic pathway glioma. See text for specifics.

long-awaited breakthrough. Biopsies may be useful for the molecular diagnosis of tumor characteristics that may have prognostic or therapeutic consequences.^{36,39,40} These analyses, although not yet included in routine clinical practice, are proving valuable, and we expect them to be essential for making therapeutic decisions and estimating prognosis in the near future.

36.8.2 Surgery

Clinical series describing surgical results for OPG usually comprise small numbers of patients, with vague inclusion criteria, no control groups, and poor follow-up. The current situation includes wide variations between different centers and groups with regard to the threshold for open surgery.

Tumors confined to the ON are considered for resection if the patient has progressive proptosis or intractable pain in a blind eye. These tumors can be approached via unilateral frontal craniotomy and orbitotomy or through the eye, especially when enucleation of the entire eye is warranted. Globe-sparing resection is also possible. It should be noted that sectioning the nerve close to the chiasm risks damage to the advancing nasal fibers (Wilbrand's knee) from the contralateral eye.

The surgical management of chiasmatic/hypothalamic tumors is even more controversial. Radical resection in a patient with viable eyesight is usually not recommended because of the susceptibility of the surrounding neural structures (hypothalamus and brainstem). In addition, there is a high risk for damage

to the optic apparatus. Subtotal resection of tumors that grow outside the visual system, such as in the third ventricle or the anterior and lateral subarachnoid spaces, can be performed for a subset of large suprasellar lesions.⁴¹ Chiasmatic/hypothalamic lesions may be approached via interhemispheric transcallosal, subfrontal pterional, subtemporal, or bifrontal interhemispheric translamina terminalis routes, depending on the direction and extent of the tumor. Combination approaches may also be used for more extensive lesions. Image guidance facilitates accurate navigation and the avoidance of damage to critical structures. Hydrocephalus may respond to decompression alone but may also require shunt placement in many cases. Ascites secondary to ventriculoperitoneal shunting in patients with chiasmatic tumors is common and may require diversion of the CSF to the atrium rather than to the abdomen.⁴² Large cystic components containing mucinous fluid are common and may require multiple resections and drainage procedures. Shunts placed within these cysts tend to malfunction after a short period of time; Ommaya reservoirs may be used in these situations for intermittent tapping and drainage.

36.8.3 Chemotherapy

Chemotherapy is considered the first line of treatment in most cases of children with progressive OPG.

"Gentle chemotherapy" with vincristine and carboplatin was introduced in 1988 by Packer et al and is now an accepted

first-line treatment.⁴³ This regimen reported PFS rates of 75% at 2 years and 68% at 3 years for chiasmatic tumors.⁴³ Carboplatin alone may also be effective in OPG treatment, with a short-term PFS rate of 83% and disease stabilization in 85%.⁴⁴ Weekly vinblastine is also frequently used as a first-line treatment or in patients with carboplatin allergies.⁴⁵ A new protocol of bevacizumab and irinotecan has shown preliminary effectiveness in the treatment of recurrent low-grade gliomas.⁴⁶ Mammalian target of rapamycin (mTOR) is an important part of the Ras pathway, which is hyperactivated in NF-1 and is considered a potential target for inhibition. So far, protocols that include mTOR inhibitors, such as a recent erlotinib (Tarceva; Genentech, South San Francisco, CA) and rapamycin protocol, have been only mildly effective.⁴⁷ Clinical trials with other mTOR inhibitors such as RAD001 (everolimus) are ongoing.

Several papers published in recent years have shown disappointing results for visual outcome following chemotherapy for OPGs.^{48–50} In many patients, despite some success in achieving structural tumor control, there was no improvement and even further decline in visual ability. Others, such as Fisher et al, have provided somewhat better results for visual prognosis with chemotherapy treatment, but for a relatively short follow-up time, providing results only after first-line chemotherapy and only for patients with NF-1.⁵¹

In addition to anatomical tumor response, chemotherapy has shown benefits in preserving intellectual function in comparison with radiation, and in controlling diencephalic syndrome.^{52,53}

36.8.4 Radiation

With the establishment of chemotherapy as the first-line treatment of choice for low-grade gliomas in general, and for OPGs specifically, the use of radiation has lessened significantly. The long-term negative consequences of radiation, especially in young patients and even more so in patients with NF-1, have made radiation an alternative used only as a last resort.

In children younger than 3 years old, radiation is contraindicated because of unacceptable cognitive impairment. In older children without NF-1, radiation may be effective for OPGs that are progressive despite chemotherapy, for metastatic tumors, or for unresectable tumors. With the usual dose of 45 to 60 Gy in 1.6- to 2-Gy fractions, 5-year PFS and overall survival rates are reported to be in the range of 82 to 85% and 93 to 94%, respectively.⁵⁴ A modest beneficial effect on visual ability was also reported.^{55,56}

The main reason for discouraging radiation therapy for OPG is its multiple long-term adverse effects. These are especially apparent in the NF-1 population. In the generic OPG population, even children older than 3 years who received radiation therapy experienced cognitive side effects.⁵⁷ Endocrine dysfunction occurs in 39 to 55% of patients treated with irradiation.^{55,57–59} In a large series of 69 patients treated before the chemotherapy era, published by Cappelli et al in 1998, approximately 15% of patients treated with irradiation had cerebrovascular complications. In the same series, approximately 30% of patients treated with irradiation at a young age had severe intellectual disabilities.⁵⁶ In the NF-1 population, the two main long-term effects of radiation are moyamoya syndrome⁶⁰ and secondary CNS malignancies. In a series of 28 patients treated

with irradiation described by Kestle et al, 5 (18%) developed moyamoya syndrome. In this same series, 60% of patients with NF-1 developed moyamoya syndrome.⁶¹ Secondary malignancies (such as malignant peripheral nerve sheath tumors) occur in 50% of patients with OPG and NF-1 who receive irradiation, as opposed to 20% of patients who do not receive irradiation. There is an increased relative risk (threefold) for the NF-1 OPG group treated with irradiation.⁶² In addition, irradiation tends to induce anaplastic changes in the original glial tumor. In one series dealing with low-grade gliomas, 16% of patients treated with irradiation developed anaplastic changes, as opposed to none in the group that did not receive radiation.⁶³

Stereotactic radiosurgery has been tested as a possible treatment for OPG, with some promising results. In several small series, good tumor control was achieved, improvement in vision was noted, and side effects were rather small.^{64,65} Some of the serious adverse effects associated with radiation may be technique-dependent, and the further examination of newer, safer techniques is warranted, especially when the rather low efficacy of chemotherapy in improving and preserving visual ability is considered. Gamma knife and proton beam therapy may also prove to be useful tools in the future.^{66–68}

36.9 Outcome

OPG outcome is generally favorable. Long-term survival rates are excellent, ranging from 80 to 96% in numerous series over the last 10 years.^{10,16,28} In an older series from 1993, the overall 10-year survival rate was 84%, with anterior tumors (nerve and chiasm) having a 10-year survival of 95% and posterior tumors a 10-year survival of 76%.⁶⁹ PFS rates vary and are considered to be about 50% depending on location, background, and the need for treatment. In the same series from 1993, PFS at 10 years was 80% for tumors of the nerve and chiasm and 59% for tumors spreading outside the chiasm.⁶⁹

From our own experience, approximately 25% of patients with OPG referred to a tertiary center require therapy; of this group, approximately 75% will need to receive second-line treatment.⁴⁸ These numbers, higher than accepted numbers in the literature, are biased because of the more aggressive nature of the tumors seen by a pediatric neurosurgeon. Various factors described in the literature as having an effect on prognosis⁷⁰ are summarized in ► Fig. 36.8.

Because of the big difference between long-term survival and PFS, as well as the heterogeneity of the patients, the long-term follow-up of patients with OPG is necessary. In addition, the discrepancy between functional outcome and anatomical outcome makes prospectively estimating the outcome of an individual patient with OPG even more difficult.

36.10 Conclusion

The goal of visual control in OPG has not yet been reached. Further understanding of the different OPG subgroups and the underlying pathophysiology of visual loss is required to treat these patients effectively and individually. Large multicenter prospective studies aimed at examining new treatment modalities are desperately needed to improve this front.

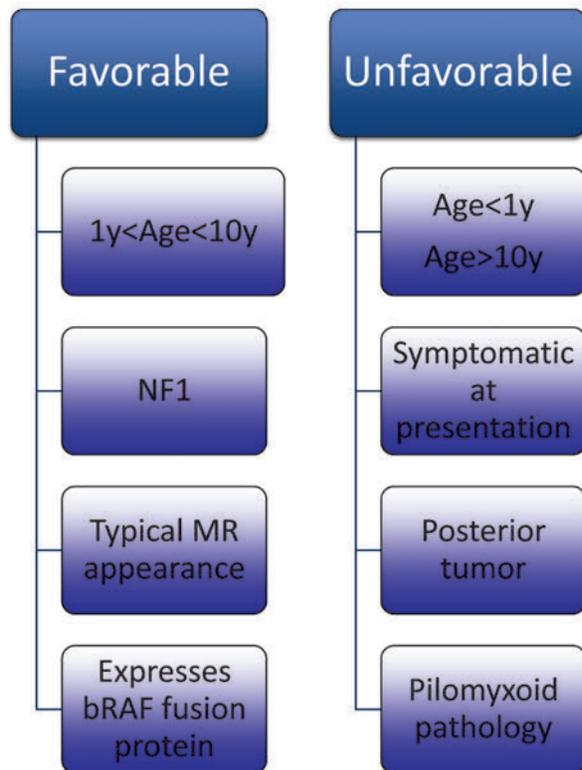


Fig. 36.8 Favorable versus unfavorable prognostic factors.

Pearls

- Bilateral optic nerve gliomas are pathognomonic for NF-1.
- Careful and close radiologic and clinical follow-up is the recommended initial approach for neurologically intact patients.
- Consider obtaining tissue for molecular analysis in selected cases.
- Treatment is usually indicated only when clear radiologic or visual progression is documented.
- The initial treatment of choice is chemotherapy.
- Surgery is reserved for orbital tumors in the setting of a blind or proptotic eye and for exophytic chiasmatic/hypothalamic tumors that cause mass effect or hydrocephalus or have a large cystic component.
- Radiation should be avoided in patients with NF-1. For sporadic OPGs, radiation can be selectively used in children older than 10 years or if chemotherapy fails to control tumor growth.

36.11 Acknowledgment

The previous version of this chapter by Cian James O'Kelly and James T. Rutka served as a basis for this version. We thank them for their contribution.

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37 Craniopharyngiomas

Jeffrey H. Wisoff and Bernadine Donahue

Cushing graphically described craniopharyngiomas as “the kaleidoscopic tumors, solid and cystic which take their origin from epithelial rests ascribable to an imperfect closure of the hypophyseal or craniopharyngeal duct” and whose management is “one of the most baffling problems to the neurosurgeon.”¹ The benign histology of these tumors is often in marked contrast to their malignant clinical course in children. The location of craniopharyngiomas, which have an intimate association with the visual pathways, hypothalamus, and limbic system, predisposes patients with these tumors to severe visual, endocrine, and cognitive deficits, both at presentation and as a result of treatment. Although most children can compensate for neurologic deficits and endocrinologic deficiencies, the cognitive and psychosocial sequelae may be functionally devastating, interfering with education, limiting independence, and adversely affecting the quality of life as the children approach adulthood.²

37.1 Epidemiology

Craniopharyngiomas constitute approximately 3% of all intracranial neoplasms.^{3,4} They are the most common nonglial tumor of childhood, accounting for 6 to 9% of pediatric brain tumors.⁵⁻⁷ Although craniopharyngiomas comprise a significant proportion of pediatric brain tumors, on a population basis they are rare. Based on an analysis of three population-based cancer registries, the incidence of craniopharyngioma in the United States is between 0.13 per 100,000 and 0.18 per 100,000 per person-years.⁸ A bimodal distribution by age has been noted, with peak incidence rates in children and among older adults. Among children, the incidence is greatest between the ages of 6 and 10 years, followed by the ages of 11 and 15 years.^{8,9} From 33 to 54% of all craniopharyngiomas occur in the pediatric age group,^{6,8,10-14} with approximately 96 to 145 new cases annually occurring in children from 0 to 14 years of age.

Although there does not appear to be any racial or ethnic predilection for craniopharyngiomas, the influence of gender is unclear. After all the data are considered, craniopharyngioma may occur slightly more often in boys.^{8,13,15-17}

Stiller and Nectoux¹⁸ have reported that the proportion of brain tumors that are craniopharyngiomas varied substantially among different global regions: 1.5% in Australia, 4.7 to 7.9% in Europe, 3.9% in Japan, 2.7% (Caucasians) and 4.9% (African Americans) in the United States, and 11.6% in Africa. Although this international variation in occurrence has led to speculation regarding environmental influences, the data must be interpreted with caution because socioeconomic conditions preclude the population-based reporting of all brain tumors in developing countries.

37.2 Pathology

Craniopharyngiomas develop from epithelial nests that are embryonic remnants of the Rathke pouch located on an axis extending from the sella turcica along the pituitary stalk to the

hypothalamus and floor of the third ventricle.^{4,19} Craniopharyngiomas gradually enlarge as partially calcified solid and cystic masses predominantly in the suprasellar region, and the cystic component can reach several centimeters. They extend along the path of least resistance into the basal cisterns or can invaginate the third ventricle. With continued growth superiorly into the third ventricle, hydrocephalus may develop.

Craniopharyngiomas have two basic patterns of cellular growth: adamantinomatous and papillary.^{3,4,10,14,20,21} Mixed tumors with both adamantinomatous and squamous papillary components or combinations of craniopharyngioma and Rathke cleft cysts can occur.^{3,4,10,14,20-23}

The adamantinomatous tumors are the most common variant, occurring at all ages. They resemble the epithelium of tooth-forming tumors, containing three distinct components: a basal layer of small cells; an intermediate layer of variable thickness with loose, stellate cells; and a top layer facing the cyst lumen, where the cells are abruptly enlarged, flattened, and keratinized. At the cyst surface, desquamated epithelial cells are present either singly or in characteristic stacked clusters (keratin nodules). These nodules may undergo mineralization with the accumulation of calcium salts, which in rare instances progresses to metaplastic bone formation. The cysts in adamantinomatous craniopharyngiomas usually contain an oily liquid composed of this desquamated epithelium, which is rich in cholesterol, keratin, and occasionally calcium.

Squamous papillary craniopharyngiomas occur nearly exclusively in adults and tend to involve the third ventricle.²⁴ They consist of solid epithelium, without loose stellate zones, in a papillary architecture resembling that of metaplastic respiratory epithelium.^{4,10,21,24} They are predominantly solid and rarely undergo mineralization. When cysts occur, the fluid is less oily and dark than in adamantinomatous tumors. As a result of the absence of calcification and minimal cyst formation, complete curative surgical resection may be obtained more often than with adamantinomatous or mixed craniopharyngiomas.^{10,17,23} Histology does not affect the risk for recurrence after subtotal resection or the response to radiation therapy (RT).

Microscopic islets or “fingers” of adamantinomatous tumor embedded in densely gliotic parenchyma are frequently seen when the tumor arises in the region of the tuber cinereum, hypothalamus, and floor of the third ventricle.^{21,23,25-29} The gliotic reaction of Rosenthal fibers and fibrillary astrocytes, varying between several hundred microns to millimeters in thickness,²⁶ effectively separates tumor from brain, thus providing a safe plane for surgical dissection.^{12,23,28,30} The presence of this gliotic tissue on surgical pathology is associated with a decreased risk for recurrence following a gross total tumor resection.²³

37.3 Radiology

The role of neuroimaging is to establish a preoperative diagnosis and then define the location and extent of the cystic, solid, and calcified portions of the tumor and its relationship to the

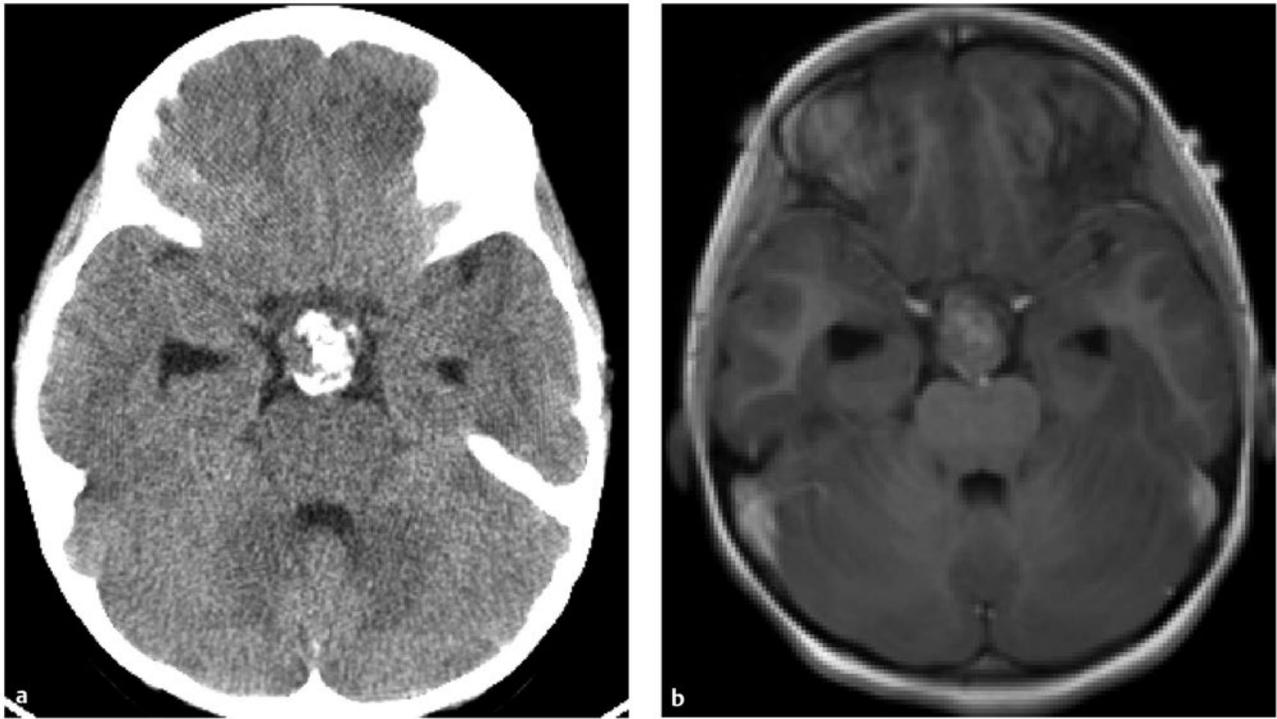


Fig. 37.1 (a) Noncontrast computed tomographic (CT) scan demonstrating calcified portion of tumor. (b) Corresponding contrast-enhanced T1 axial magnetic resonance image. Note the nonenhancing portion, representing the calcification seen on CT.

distorted normal anatomy. Radiographic evaluation includes computed tomography (CT), magnetic resonance (MR) imaging, MR angiography, and, where available, MR spectroscopy.^{31–33} Vascular anatomy can be well demonstrated by MR imaging and MR angiography, obviating the need for invasive cerebral angiography.³²

CT and MR imaging have complementary roles in the diagnosis of craniopharyngiomas^{31,32,34} (► Fig. 37.1). CT is superior in the detection of the varied and complex calcifications. Noncontrast CT usually demonstrates a suprasellar and often intrasellar mass with calcifications, as well as hypodense solid and cyst components. The low density of the cystic component is usually greater than the attenuation of cerebrospinal fluid (CSF). A small percentage of craniopharyngioma cysts may be of high density.³¹ CT shows secondary changes in the skull base, such as enlargement of the sella turcica and/or erosion of the dorsum sellae. When MR imaging is available, contrast-enhanced CT is unnecessary.

MR imaging and MR angiography provide valuable information about the relationships of the tumor to surrounding structures, delineating the involvement or displacement of the visual pathways, hypothalamus, ventricles, and vessels of the circle of Willis. Noncontrast sagittal T1-weighted images may show the normal pituitary, leading to the correct diagnosis.³⁴ Fine calcifications may not be visible, demonstrating a paradoxically increased signal on T1 imaging or, if more substantial, exhibiting characteristic signal voids. Craniopharyngioma cysts are uniformly bright on T2-weighted sequences; however, on T1-weighted sequences, the signal intensity of the fluid may range

from hypointense to hyperintense,^{31,32,35} reflecting the heterogeneous contents. The correlation between MR imaging and the biochemical composition of cyst fluid is complex, with protein, lipid, and iron concentrations having a major influence on cyst signals.^{32,36} Cyst capsule and solid tumor vividly enhance with contrast.

Noncalcified solid craniopharyngiomas may have CT and MR imaging characteristics that are indistinguishable from those of other pediatric suprasellar neoplasms, including chiasmatic hypothalamic gliomas, germinomas, and pituitary adenomas. Proton MR spectroscopy demonstrates unique spectroscopic profiles that differentiate these tumors.³³ Craniopharyngiomas show a dominant peak, consistent with lactate or lipids, and only trace amounts of other metabolites. In contrast, gliomas demonstrate choline, *N*-acetylaspartate, and creatine, with an increased ratio of choline to *N*-acetylaspartate compared with that of normal brain; pituitary adenomas show choline peaks or no metabolites at all.

The surgeon's impression of the extent of tumor resection must be confirmed by neuroimaging. Postoperative imaging with both enhanced MR imaging and CT is best done within 48 hours to avoid the artifacts of surgical trauma.³² Residual tumor should be graded according to the method of Hoffman³⁰: grade 1, no residual tumor or calcification; grade 2, tiny (<1 mm) fleck of calcification without evidence of enhancement or mass; grade 3, small "calcific chunk" without enhancement or mass effect; grade 4, small contrast-enhancing lesion without significant mass effect; and grade 5, contrast-enhancing mass.

37.4 Clinical Presentation

In children, the slow growth of craniopharyngiomas often results in a delay between the onset of symptoms and diagnosis, with a typical prodrome of 1 to 2 years.^{37,38} The main presenting signs and symptoms of craniopharyngiomas are related to pressure upon adjacent neural structures.^{6,9,23,29,37,39–45} Headache from raised intracranial pressure is the most common complaint, occurring in 60 to 75% of cases. Visual symptoms are noted in approximately half of children. Progressive visual loss is often well tolerated by children and not diagnosed until they are noted to be sitting progressively closer to the television. Evidence of hormonal insufficiency, including growth failure, delayed sexual maturation, excessive weight gain, and diabetes insipidus, is present in 20 to 50% of children at diagnosis but is rarely the reason why a child is brought to medical attention. With progressive growth into the frontal lobes and hypothalamus and/or the onset of hydrocephalus, psychomotor slowing, apathy, and short-term memory deficits may also occur, with a decline in academic performance.

Formal preoperative neuro-ophthalmologic, endocrinologic, and neuropsychological evaluations are mandatory. On preoperative testing, 70 to 80% of children will demonstrate abnormal visual acuity or fields.^{9,23,29,37,39,46} The specific ophthalmologic deficits reflect the direction of growth of the tumor and its compression of various portions of the visual apparatus: prechiasmatic extension will compress the optic nerves, with a loss of visual acuity, whereas posterior tumors will cause chiasmatic compression, with complex visual field defects. Frank papilledema is present in approximately 20% of children.³⁸

Fewer than 30% of children are endocrinologically normal at diagnosis.^{44,45,47–49} Growth hormone deficiency is the most common finding, present in up to 75% of children. Gonadotropin deficiency is observed in up to 60% of children, and thyroid or adrenal dysfunction in approximately one-third. Diabetes insipidus is relatively uncommon preoperatively, occurring in 9 to 17% of patients.

The essential preoperative endocrine testing includes an evaluation of adrenal function and thyroid function and an assessment of salt and water balance before the initiation of steroid therapy; measurement of gonadotropins and growth hormone is also routinely performed. Failure to preoperatively recognize and correct adrenocorticotropic hormone (ACTH) or thyroid hormone deficiency or appropriately manage diabetes insipidus can result in severe morbidity or death.

37.5 Treatment

Although the optimal treatment of craniopharyngiomas remains controversial, permanent tumor control or cure should be the goal for pediatric craniopharyngiomas. At the center of the debate over potentially curative therapeutic modalities are the extent of surgical excision and the role of cranial irradiation. Total resection of the tumor has been advocated by many centers, whereas others have elected to treat with minimal surgical resection followed by RT. Palliative therapies may provide temporary relief from symptoms; however, progressive solid and cystic tumor growth is inevitable. The management of craniopharyngiomas that have failed primary therapy is associated with significantly increased morbidity and mortality.

Although most physicians would agree that complete removal is desirable for a benign tumor, the tendency of craniopharyngiomas to adhere to adjacent neural tissue and the vessels of the circle of Willis makes excision technically difficult and increases the chance of morbidity and mortality.^{16,50} In order to avoid perioperative hypothalamic damage, some surgeons prefer to perform a subtotal resection or limited surgery.^{51,52} Because partial surgery alone will nearly invariably result in tumor recurrence,^{41,53,54} adjuvant postoperative irradiation is employed to maximize tumor control. Overall, survival rates among patients treated by these two treatment methods have been comparable.^{9,16,43,51,52,54–59}

It is important to point out, however, that the quality of survival after each of these approaches has not been thoroughly documented, even though such information would provide important feedback about the efficacy of these treatment modalities. Much of the follow-up research has focused on physical morbidity, often at the exclusion of the behavioral, emotional, and cognitive sequelae that can negatively impact quality of life.

37.5.1 Surgery

Most pediatric neurosurgeons in North America and Europe favor complete microsurgical resection as the treatment of choice for newly diagnosed craniopharyngiomas.^{9,12,23,37,41,54,57,60–62} The feasibility and success of radical resection depend on the availability of surgical expertise and postoperative endocrinologic support. They also depend on an understanding of the size and extent of the tumor, whether the tumor is primary or recurrent, the clinical condition of the patient, and the societal resources available to cope with potential postoperative deficits. If the socioeconomic conditions applicable to an individual patient do not provide appropriate long-term endocrinologic support and neurologic care, functional morbidity may overshadow the merits of curative resection.

Proponents of radical surgery argue that the advances in microsurgical techniques have facilitated the treatment of these lesions, and that substitutive therapy can mediate the endocrinologic sequelae secondary to hypothalamic injury. The greater immediate morbidity of this approach may be mitigated by the fact that RT carries risks for unpredictable late neurologic, vascular, and oncogenic side effects, as well as the long-term development of neuropsychological deficits in children within the domains of intelligence, attention, memory, and psychomotor processing speed; the most salient factors increasing these risks are young age at irradiation and total dosage.^{56,63–66}

Operative Technique: Craniotomy

A categorization of the pattern and extent of growth assists in evaluating treatment options and potential surgical approaches, and in predicting outcome. Several different clinical–radiologic classification systems have been proposed^{9,30,37,38,67}; all attempt to describe the degree of vertical and horizontal extension, displacement of the optic nerves and chiasm, number of anatomical regions involved by the tumor, and overall size of the tumor. Size is graded as small (2 cm), medium (2 to 4 cm), large (4 to 6 cm), and giant (>6 cm)⁹ (► Fig. 37.2). Giant tumors may extend into multiple or all compartments, extending from the medulla to the foramen of Monro.

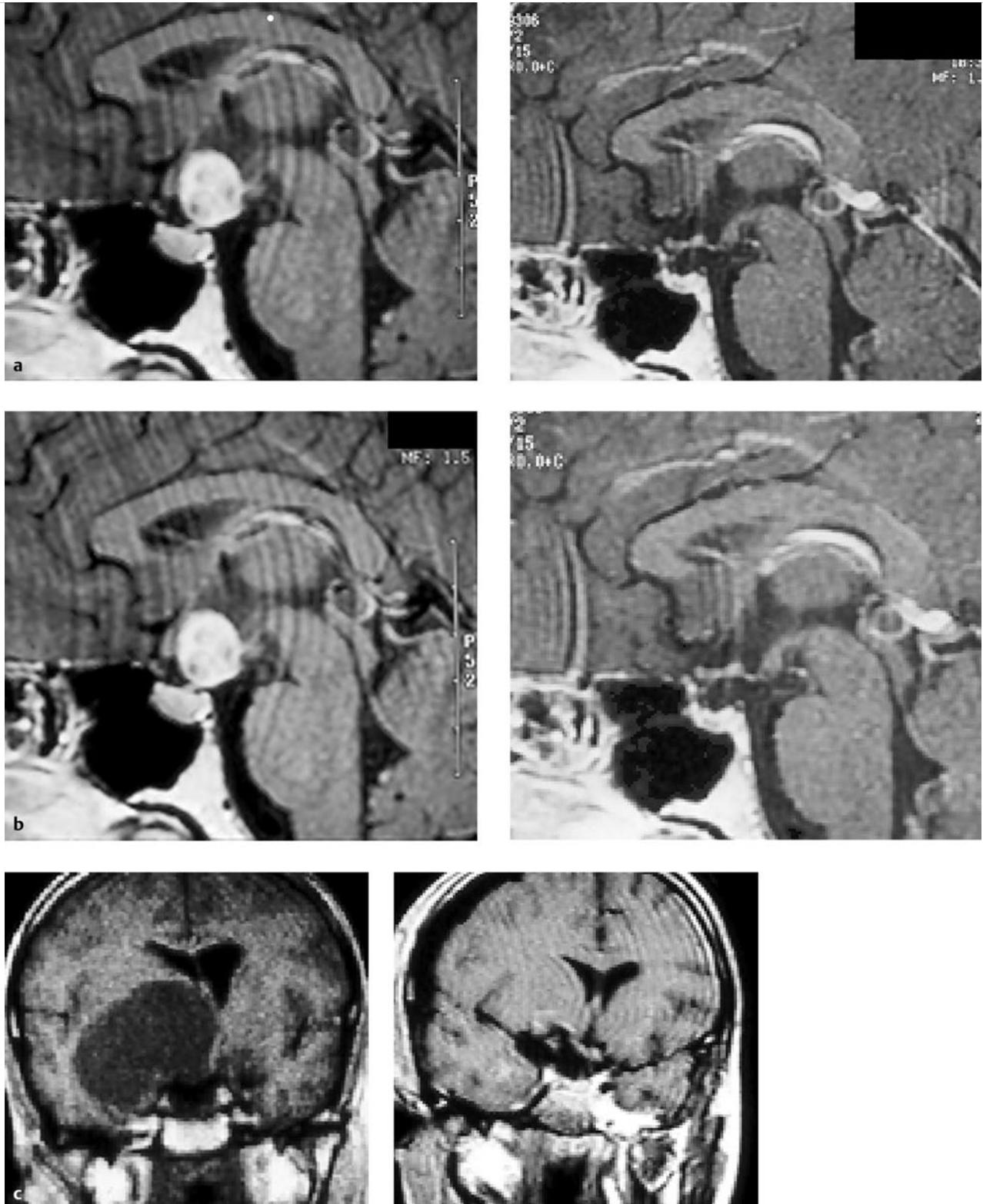


Fig. 37.2 (a) Pre- and postoperative magnetic resonance (MR) images of a small (2 cm) craniopharyngioma. (b) Pre- and postoperative MR images of a medium (4 cm) craniopharyngioma. (c) Pre- and postoperative MR images of a large (5 cm) craniopharyngioma. (continued)

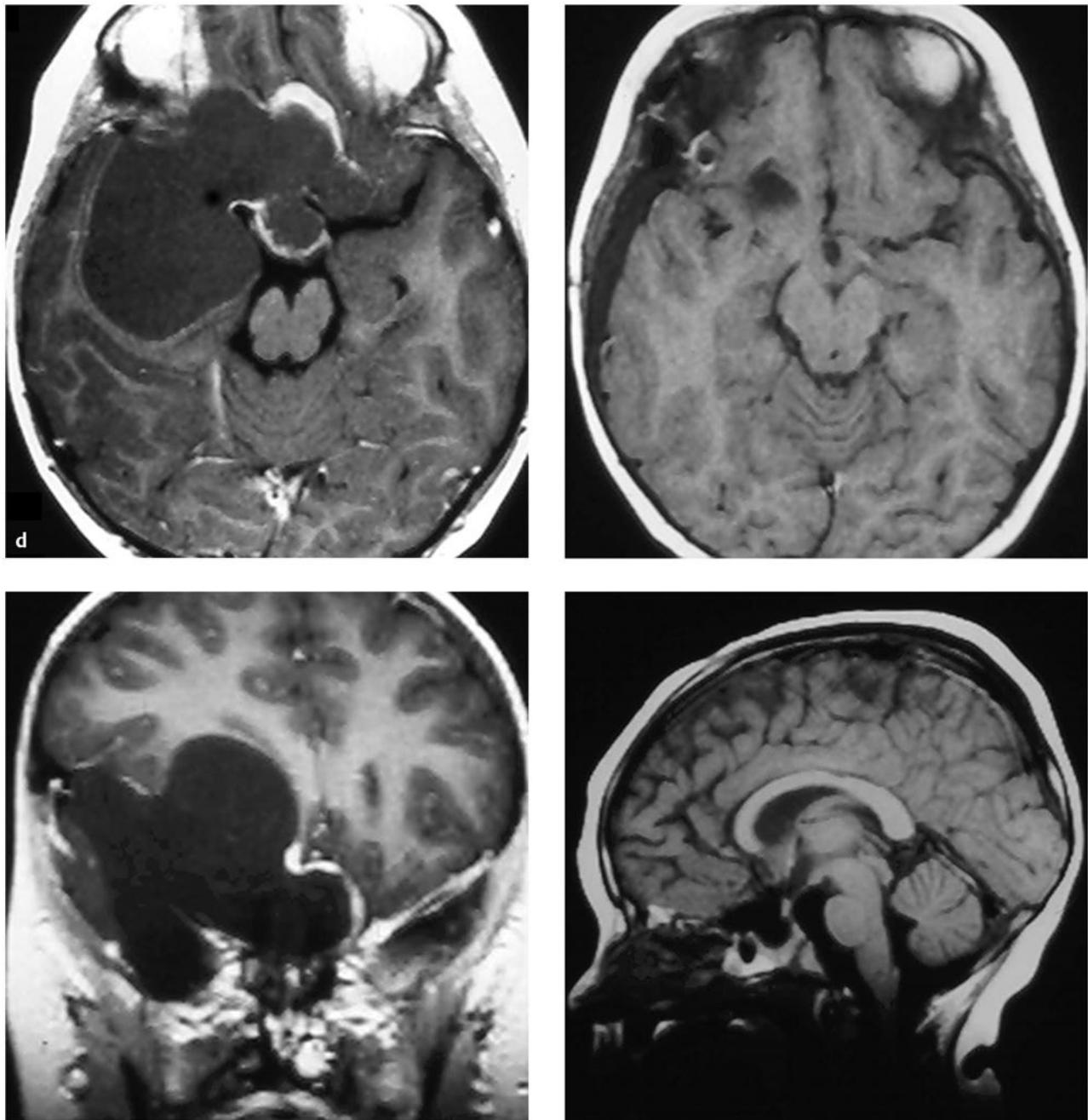


Fig. 37.2 (continued) (d) Pre- and postoperative MR images of a giant (7 cm) craniopharyngioma.

A variety of operative approaches have been described and championed by different surgeons, including the subfrontal,^{6,12,28,68} pterional,^{9,69,70} bifrontal interhemispheric,^{71,72} subtemporal,⁷³ transcallosal,¹⁷ and transsphenoidal approaches.^{70,74–77} Modified skull base techniques expanding on the pterional approach, including orbitofrontal and orbitozygomatic approaches, have gained popularity over the past two decades.^{54,62} Surgical adjuncts, including ultrasonic aspirators, frameless stereotaxy, and rigid and flexible neuroendoscopes, should be available and utilized when appropriate.

The senior author prefers a skull base modification of the pterional craniotomy,⁹ with the additional removal of the supraorbital rim, anterior orbital roof, and zygomatic process of the frontal bone. This approach offers the shortest, most direct route to the suprasellar region and minimizes or eliminates the retraction of normal brain. Tumors extending from the pontomedullary junction (► Fig. 37.2d) to above the foramen of Monro can be removed through the pterional approach. In no patient is a cortical resection⁷⁸ or sacrifice of the olfactory nerve³⁰ necessary.

Dexamethasone (0.1 mg/kg), phenytoin (15 mg/kg), and cephalexin (25 mg/kg) are administered after induction and intubation. Mannitol (0.25 g/kg) is then given at the time of skin incision to help maximize brain relaxation. The diuretic effect is maximal within the first hour of surgery, long before manipulation of the pituitary stalk and hypothalamus may produce the diabetes insipidus that complicates fluid and electrolyte management. Before the dura is opened, either intraoperative ultrasound or frameless stereotaxy is used to determine the location and extent of the tumor and its relationship to the operative exposure.

Throughout the surgery, retraction of the brain is minimized. Mannitol, hyperventilation, and gradual drainage of the CSF through the opened sylvian fissure and basal cisterns will usually provide excellent relaxation, even in the presence of moderate degrees of hydrocephalus. Ventricular drainage is reserved for cases refractory to these maneuvers or when the use of an intraventricular endoscope is anticipated (*vide infra*). Although hydrocephalus is present in 15 to 66% of patients,^{9,12,23,37,43,69,72,79} preoperative shunting is reserved for patients with severe symptoms of increased intracranial pressure that is unresponsive to medical management.

Because these tumors often extended diffusely throughout the suprasellar cisterns, displacing and distorting normal structures, identification of the vascular anatomy provides essential landmarks. Starting laterally, the sylvian fissure is widely split, and the distal branches of the middle cerebral artery are identified. The arachnoidal dissection proceeds medially to the main trunk of the middle cerebral artery, which is followed proximally to the ipsilateral carotid bifurcation, anterior cerebral artery, and internal carotid artery. As the carotid is followed proximally to the clinoid, the optic nerve, chiasm, and/or tracts are identified in relation to the tumor.

The premature decompression of a craniopharyngioma, especially a cystic tumor, causes the tumor capsule and arachnoid to become redundant, obscuring the planes of dissection. Working in the prechiasmatic, optic-carotid, and carotid-tentorial triangles, the surgeon develops and maintains an arachnoidal plane between the intact tumor and the branches of the ipsilateral carotid and vessels of the circle of Willis, preserving all of the vessels and their perforating branches. This plane is developed posteriorly until the basilar artery is identified. In primary tumors, the membrane of Lilliequist invariably separates the tumor from the basilar artery.

Once the vascular anatomy had been identified and separated from the tumor, the cyst is aspirated and the solid internal component debulked. Care is taken to preserve the capsule of the tumor. Again with the surgeon working in the parachiasmatic spaces and maintaining arachnoidal planes, the tumor is progressively dissected free from the optic nerves, the contralateral carotid and its branches, and the inferior aspect of the optic chiasm. An attempt is always made to identify and preserve the pituitary stalk; this can be accomplished in 20 to 30% of the patients. When the stalk cannot be separated free from the tumor, it is sectioned as distally as possible to prevent undue traction on the hypothalamus. After the tumor is dissected free from the entire circle of Willis, the pituitary stalk, and the optic apparatus, the capsule is grasped, and with continuous traction and blunt dissection, the gliotic plane is developed, which allows the tumor to be delivered from its attachment to the

hypothalamus in the region of the tuber cinereum. After the tumor is removed, the entire bed must be inspected for inadvertent residual disease. A micromirror or angle endoscope is used to view the undersurface of the chiasm and hypothalamus to confirm a complete resection.

If the tumor extends into the third ventricle or has a significant retrochiasmatic component, the lamina terminalis is fenestrated. The lamina terminalis is easily distinguished from the chiasm, appearing pale, avascular, and often distended by tumor. As retrochiasmatic tumor is removed, the prechiasmatic space may widen, allowing an additional avenue for dissection.

A third ventricular tumor is simultaneously delivered through the lamina terminalis as well as from below the chiasm. Placement of a 2.3-mm neuroendoscope into the lateral or third ventricle assists in monitoring the delivery of the intraventricular component of the tumor. With the endoscope, simultaneous or sequential transcallosal exposure of the intraventricular tumor¹⁷ is usually not obligatory.

When the tumor extends into the sella turcica, removal of the posterior planum sphenoidale and tuberculum sellae may be required to gain adequate intrasellar exposure.⁶⁸ After removal of tumor, any defects communicating with the sphenoid sinus must be obliterated with fat and pericranial grafts.

Operative Technique: Transsphenoidal/Transnasal Surgery

Although most craniopharyngiomas of childhood arise in the region of the tuber cinereum, a small percentage originate from more caudal craniopharyngeal duct cell rests within the sella turcica.⁷⁵ As these tumors grow, the diaphragma sellae stretches over the dorsal aspect, separating it from suprasellar structures and preventing tumor adherence to the optic apparatus, hypothalamus, and vessels of the circle of Willis. This feature of the pathologic anatomy allows a radical removal of infradiaphragmatic intrasellar tumors through a transsphenoidal/transnasal approach.^{17,70,74,75,80} From 3 to 15% of pediatric craniopharyngiomas may be amenable to transsphenoidal/transnasal resection.^{37,81}

Transsphenoidal/transnasal surgery in young children may present anatomical difficulties related to the small size of the bony structures and to the lack of a pneumatized sphenoid sinus. The presence of a conchal or pre-pneumatized sphenoid sinus is not a contraindication to transsphenoidal surgery; however, the bone must be meticulously drilled or chiseled under fluoroscopic control to obtain wide access to the sella turcica.⁷⁵ Thick bones of the sinuses and skull base may require drilling near the sella, planum, and optic nerves. Abe and Lüdecke⁸² reported that incompletely pneumatized sphenoid sinuses required drilling in 46% of patients in their series of 11 children, but this did not hinder resection in any case. We recommend using an irrigating drill with a diamond bur when the bones of the skull base are drilled to decrease the risk for thermal or mechanical injury to the optic nerves, chiasm, and internal carotid arteries. Other useful adjuncts include a micro-Doppler probe to better identify the carotid artery and stereotactic image guidance with high-resolution CT in addition to standard preoperative MR imaging.

As noted by Im and colleagues,⁸³ the poorly pneumatized sinuses and smaller facial structure of children create an even

narrower working corridor. They accomplished gross total resection of six large craniopharyngiomas via the transsphenoidal approach by relying on the cystic nature of all six tumors, the infradiaphragmatic origin of the tumors, and the use of micro-mirrors for lateral visualization. They noted that predominantly cystic tumors are more common in adults than in children, and early decompression can aid in the extirpation of such tumors and removal of the capsule from surrounding structures. With the advent of angled endoscopes and improved optics, micro-mirrors will likely become obsolete. Nevertheless, taking advantage of the cystic nature of craniopharyngiomas is a critical surgical pearl that facilitates transsphenoidal/transnasal surgery via a long, narrow corridor.

Other technical aspects of the operation do not differ significantly from those for similar surgery in adults, particularly in regard to the overall approach and tumor resection^{69,70,75,77,84} however, because of the rarity of these tumors, this approach should be utilized only by surgical teams with adequate experience.⁸⁵

After a wide dural opening, the normal, ventrally displaced pituitary gland is encountered. If the gland obstructs the visualization of the tumor, the pituitary gland should be incised in the midline, then gently pushed laterally to obtain exposure of the dorsally located craniopharyngioma. Once an initial plane of cleavage between the tumor and sellar wall is established, the capsule is opened, with drainage of cyst fluid and debulking of solid neoplasm. Following this internal decompression, the capsule is dissected from the walls of the cavernous sinuses and pituitary gland to complete mobilization of the intrasellar tumor. When the superior capsule adheres to the diaphragma, it must be incised and resected. As the superior craniopharyngioma is delivered, the remaining attachment of the tumor to the pituitary stalk is visualized and detached with bipolar coagulation and sharp dissection to achieve a gross total resection. Resection of the diaphragma invariably produces an intraoperative CSF leak. Obliteration of the sella and sphenoid sinus with a free fat graft is mandatory. Several days of postoperative lumbar drainage is recommended.⁷⁰

Outcomes of Surgery

Craniotomy

Radiographically confirmed total resection can be accomplished in 80 to 100% of primary tumors in children.^{9,12,23,37,54,60–62,72} Following radiographically confirmed total resection (Hoffman grade 1 or 2), no adjuvant therapy is administered.⁸⁶ Accessible tumor demonstrated on postoperative MR imaging or CT that was inadvertently left unresected at primary surgery should be removed. A second operation within several weeks of a primary surgery does not entail any significant added risks or technical difficulty. Recurrence rates following total resection range from 0 to 20% (► Table 37.1).^{9,12,23,37,54,57,60} Most recurrences in children develop within 2 to 3 years.^{9,12,23,37,60,87–89} Tumor recurrence may be distant from the primary site as a result of implantation at the time of initial resection,^{60,90,91} and this has been seen in 7% of recurrent tumors treated by the senior author.⁹² Reoperation can be curative, especially with solid tumors; however, scarring from previous surgery may increase the technical difficulty of surgery (vide infra).

Table 37.1 Recurrence after primary resection

	Total number of children	Radical surgery	Recurrence	Mortality
Choux et al (1991) ³⁷	454	251	19%	4%
Fahlbusch (1997) ⁶⁹	30	13	17%	0
Hoffman et al (1992) ¹²	50	45	29%	2%
Tomita and McLone (1993) ⁶⁰	27	23	5%	0
Elliott et al (2010) ⁶²	57	57	20%	3%
Yasargil (1996) ²⁰⁸	61	61	10%	2%

The rates of perioperative mortality following radical surgery have decreased substantially in the last decade, from between 6 and 11% to between 0 and 4%.^{9,12,22,23,28,37,53,54,60,62,70,79,88,93} The philosophy²⁹ and experience of the surgeon^{23,57,79} significantly affect the likelihood of achieving a curative total resection with a low incidence mortality or disabling morbidity. Centers performing fewer than two operations for radical resection per year had a good outcome in 52% of cases, compared with 87% of cases for institutions that performed radical surgery more often.⁵⁷ In addition, the size of the tumor, severity of preoperative deficits, and presence of hydrocephalus all impact on postoperative morbidity,^{17,79} although not on disease control.⁹⁴

Younger age has historically been associated with worse outcome, regardless of the therapeutic modality. De Vile et al reported age younger than or equal to 5 years as a predictor of poor outcome after primary surgery and at long-term follow-up, and of a decreased chance of cure.⁷⁹ Rajan et al also reported a linear trend of improved disease- and treatment-related survival with increasing age in children with craniopharyngioma.¹⁶ Erşahin et al noted improved outcome and less chance of recurrence in children older than 10 years of age at the time of diagnosis.⁹⁵ Several authors have reported higher rates of tumor recurrence in children younger than 5 years.^{37,79,96,97} However, some studies reported no associations between age and outcome, survival, rates of recurrence,^{98–101} or obesity and overall health status.¹⁰²

In the senior author's experience, radical resection alone at presentation and recurrence offered disease control in 89.5% of 19 patients younger than 5 years with no operative mortality and minimal morbidity.¹⁰³ One patient developed a fusiform dilatation of the internal carotid artery and experienced a small recurrence that was successfully treated with gamma knife radiosurgery. There was one late mortality in a young child who underwent subtotal resection at New York University after having failed multiple resections, aspirations, and at outside hospitals. Although disease control was not obtained in this patient, death was secondary to an endocrine crisis unrelated to tumor progression. Overall, disease control was successfully achieved in the vast majority of our pediatric patients with surgical resection alone—avoiding the significant risks of irradiation in this young population of patients. Furthermore, we found no difference between the rates of overall survival, neurologic deficits, endocrine deficiency, hypothalamic dysfunction, and quality of life in patients 5 years or younger and those in patients older than 5 years in our entire series of 86 children.

Endocrine disturbances are common after radical resection as a result of hypothalamic manipulation and pituitary stalk sectioning.^{7,9,37,60,104,105} Endocrine morbidity may be more severe when tumor resection involves bilateral manipulation of the hypothalamus.¹⁷ Although a significant percentage of deaths in earlier series were attributable to pituitary insufficiency,^{105,106} this is uncommon today, provided adequate socioeconomic resources are available.

Hormonal replacement therapy is required in approximately 80% of the children.^{23,44,47–49,107} Thyroid and cortisol replacement therapy is administered as necessary. Diabetes insipidus is universally present immediately following surgery. Over the course of the first week, diabetes insipidus may alternate with inappropriate antidiuretic hormone release (SIADH). Meticulous attention to fluid balance and electrolyte status is essential to avoid severe fluctuations from hypernatremia to hyponatremia. Permanent diabetes insipidus will develop in approximately 75% of children.^{9,23,55} Replacement with synthetic vasopressin (DDAVP) provides excellent control of diabetes insipidus in children with an intact thirst mechanism. However, the rare combination of ADH insufficiency and an impaired sense of thirst following aggressive surgery with severe hypothalamic injury remains one of the most complex management problems.¹⁰⁴

Excess weight is often the overriding concern during long-term follow-up. As Hoffman and colleagues¹² have noted, “In a society where fitness and slim bodies are praised, obesity has led to problems with peers.” Weight gain without overt hyperphagia may occur in half of all children undergoing radical surgery, although morbid obesity with lack of satiety is far less common.^{7,37,44,45,108,109} Many children may become distraught over the alteration in habitus and body image; five of our patients have required individual or family counseling to address these psychological and emotional issues. We now routinely counsel families and older children preoperatively that they may experience a 10 to 15% permanent weight gain. Bilateral hypothalamic damage, particularly in children with larger tumors, may result in an insensitivity to endogenous leptin and a disturbed feedback mechanism from the hypothalamic leptin receptors to the adipose tissue.¹⁰⁹ Preoperative weight gain and MR imaging evidence of extensive involvement of the hypothalamus may help predict the patients most at risk for severe postoperative obesity.¹⁰⁸

Although most children with craniopharyngiomas are deficient in growth hormone, some will maintain a normal or even

accelerated growth rate after surgery, often associated with hyperphagia and obesity.^{47,48} Normal or accelerated growth following surgery does not indicate the presence of normal growth hormone secretion or ensure continued growth. A complex series of metabolic events, including the activation of insulin-like growth factor-1 by hypothalamic hyperphagia and obesity-induced hyperinsulinemia, may explain this growth pattern.^{44,110} Many later fail to maintain this growth, and if growth hormone treatment is not instituted, adult height is compromised.⁴⁷ Growth hormone treatment may be recommended in these children for long-term improved growth velocity, adult height, and other growth hormone-dependent metabolic processes.¹¹¹ Even when growth hormone replacement may not affect growth, it may help decrease body mass index.¹¹²

Total removal of the tumor offers the optimal ophthalmologic recovery and outcome.³⁷ Some degree of deterioration in visual function is present in approximately 20% of children after surgery.³⁷ Maximum improvement in visual acuity and fields is noted within the first postoperative month.⁴⁶ The extent and duration of preoperative deficits, but not age, are associated with a worse outcome.^{9,23,37,93} Visual outcome from the authors' experience and current literature is summarized in ► Table 37.2

Fusiform dilatation of the carotid artery (FDCA) occurs in 10 to 20% of children several months to years following radical surgery,^{113–115} although it is underreported in the literature. In the senior author's experience of 76 consecutive children treated with aggressive microsurgical resection of craniopharyngiomas with complete follow-up imaging, almost 10% of children experienced postoperative fusiform aneurysmal dilatation of the supraclinoid carotid artery.¹¹⁵

There have been a total of 26 reported cases of FDCA following craniopharyngioma resection in children and young adults.^{114–121} The mean age at time of surgery was 10.4 years, the mean tumor size was 3.3 cm, and the mean interval from surgery to the diagnosis of FDCA was 12.5 months. FDCA lesions stabilized in 20 of 24 cases (83%) over an average follow-up duration of 6.5 years (two lesions were treated upon initial diagnosis without serial imaging^{119,121}). All 15 lesions that have been observed for at least 5 years have stabilized in size. Only two (7.7%) cases became symptomatic (headache in one patient, vision loss from optic nerve compression in another patient). No patient experienced rupture during the follow-up period.

The pathogenesis is unclear but most likely is related to operative manipulation and retraction causing injury to the vasa

Table 37.2 Visual function after radical resection

	Hoffman et al ¹² (50 children, all primary)	Yasargil et al ⁹ (68 children, 50 primary and 16 recurrent)	Tomita and McLone ⁶⁰ (27 children, all primary)	Elliott et al ⁶² (86 children, 57 primary and 29 recurrent)
Visual field				
Improved	39%	63%	62%	26%
Stable	20%	32%	19%	55%
Worse	41%	5%	19%	19%
Visual acuity				
Improved	55%	60%	59%	16%
Stable	15%	25%	30%	69%
Worse	30%	15%	11%	15%

vasorum and subsequent weakening of the muscular layer. Although RT may have contributed to the onset or progression of FDCA in three reported cases, the majority of patients (88%) had not received RT before the onset of FDCA. The natural history of FDCA appears to be dramatically different from that of radiation-induced aneurysms,^{122–126} most of which are saccular in morphology, not fusiform. Postradiation aneurysms occurred at a mean of 10 years following treatment and presented with subarachnoid hemorrhage in over 60% of cases. The putative pathogenesis of RT-induced aneurysms is endothelial damage from the ionizing radiation; smaller vessels and capillaries are usually more affected than larger-caliber vessels.¹²⁷

The pathogenesis and natural history of radiation-induced aneurysms are markedly different from those of FDCA following craniopharyngioma surgery and should not be treated in a similar manner. Our experience is consistent with that of most other authors,^{116,120,128} that FDCA may be a relatively frequent but clinically benign complication following craniopharyngioma and should be radiographically observed. If operation is required for recurrent tumor, Sutton has recommended approaching the tumor from the opposite side.¹¹⁴ For small, recurrent craniopharyngiomas with FDCA, stereotactic radiosurgery may be a useful and safe option, with high rates of reported local control.^{129–132} Direct reconstruction of the carotid artery is dangerous and should be avoided. Whether wrapping the dilatation has long-term benefit is similarly uncertain.^{113,114} Conservative follow-up with MR imaging and MR angiography is appropriate.

Transsphenoidal Resection

Total resection can be accomplished in 60 to 90% of primary infradiaphragmatic intrasellar craniopharyngiomas; however, the rate of success drops to 10 to 60% for recurrent tumors.^{69,70,76,77,81,84} In experienced hands, operative mortality ranges from 0 to 4% and

nonendocrine morbidity from 15 to 25%, with children tending to do better than adults.^{69,70,75,77,81} The incidence of new diabetes insipidus, but not of other endocrine deficiencies, appears to be less than with transcranial surgery.^{17,69,70,84} Impairment of psychosocial function is uncommon.^{69,70} Recurrence after total resection of a primary tumor develops in 0 to 43% of patients, with the incidence of recurrence substantially less in the most experienced centers.^{69,70,76,81,84}

A recent meta-analysis of the major surgical series for the treatment of pediatric craniopharyngiomas demonstrated that the patients treated with transsphenoidal/transnasal approaches had excellent outcomes.¹³³ Compared with the children who had formal craniotomies, the patients treated with transsphenoidal/transnasal surgery had better visual, neurologic, endocrinologic, and oncologic outcomes.

Directly comparing outcomes following craniotomy and transsphenoidal/transnasal surgery for pediatric craniopharyngioma may not be valid. Critical to this analysis is the identification of baseline differences between the populations of patients selected for each surgical approach (► Table 37.3). Craniopharyngiomas treated transsphenoidally tended to be smaller, more often completely or predominantly intrasellar, and often cystic in nature.^{70,134,135} These patients also had less hydrocephalus and no reported instances of elevated intracranial pressure.

Prior studies have reported worse outcomes in patients with hydrocephalus, larger tumors, and poor preoperative functional status.^{9,62,79,136} Moreover, large tumor size has been associated with increased operative mortality,⁹ neurologic and hypothalamic morbidity,^{9,79,95} a lower probability of gross total resection,^{61,79,135} and higher recurrence rates.^{79,95,137,138} The selection bias due to these baseline differences may explain the improved outcomes in the transsphenoidal surgery group in the meta-analysis. Regardless of these findings, further experience with transsphenoidal/transnasal approaches in conjunction with

Table 37.3 Comparison of baseline characteristics and outcomes following resection of pediatric craniopharyngiomas via transcranial and transsphenoidal / transnasal approaches

Variable	Transcranial series, % (No.)	Transsphenoidal Series, % (No.)	p Value
Preoperative vision deficits	53.5% (1,051 of 1,966)	68.5% (124 of 181)	<0.0001
Preoperative hydrocephalus	41.7% (678 of 1,625)	5.1% (5 of 99)	<0.0001
Preoperative elevated ICP	42.6% (729 of 1,713)	0% (0 of 138)	<0.0001
GTR	60.9% (1,693 of 2,780)	72.1% (199 of 276)	0.0003
Recurrence after GTR	17.6% (261 of 1,518)	8.0% (16 of 201)	0.0005
Operative mortality	2.6% (68 of 2,622)	1.3% (5 of 373)	0.21
Neurologic morbidity	9.4% (200 of 2,140)	3.1% (10 of 325)	<0.0001
Diabetes insipidus	69.1% (1,437 of 2,076)	23.9% (76 of 318)	<0.0001
Vision improvement	47.7% (454 of 1,051)	85.5% (106 of 124)	<0.0001
Vision deterioration	13% (263 of 2,029)	2.3% (8 of 352)	<0.0001
Obesity or hyperphagia	32.2% (439 of 1,363)	32.1% (35 of 109)	1.00
Overall survival	90.3% (2039 of 2258)	93.9% (216 of 230)	0.075

Abbreviations: GTR, gross total resection; ICP, intracranial pressure.

Source: From Elliott RE, Jane JA Jr, Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. *Neurosurgery* 2011;69(3):630–643, discussion 643.¹³³

Table 37.4 Relative indications for and contraindications to transcranial and transsphenoidal resection of craniopharyngiomas

	Transcranial approaches	Transsphenoidal approaches
Indications	Large or gigantic tumors	Purely intrasellar tumors
	Cystic or solid suprasellar tumors	Intra- and suprasellar subdiaphragmatic tumors
	Tumor entirely within the third ventricle	Predominantly cystic tumors
Advantages	Excellent visualization and control of major arteries	Early decompression of tumor before manipulation of optic apparatus
		Shorter hospital stays
		Less tissue trauma and brain retraction
		Less pain
Contraindications	Intrasellar tumors	Tumors with extension lateral to the internal carotid artery
		Large or gigantic tumors
		Encasement of arteries of the circle of Willis or optic apparatus
		Suprasellar lesions with peripheral calcifications
Disadvantages	Brain retraction	Immature (conchal) sphenoid sinus
	Manipulation of optic apparatus before tumor removal	Poor control of hemorrhage (arterial injury)
		Risk for cerebrospinal fluid leak

Source: From Elliott RE, Jane JA Jr, Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. Neurosurgery 2011;69(3):630–643, discussion 643.¹³³

innovations in endoscopic instrumentation will undoubtedly continue to expand the indications for transsphenoidal/transnasal surgery and, ultimately, limit patient morbidity and improve overall outcomes and quality of life. ▶ Table 37.4 summarizes the relative indications, advantages, and disadvantages of the transcranial and transsphenoidal/transnasal approaches.

37.5.2 Irradiation

Despite the fact that aggressive surgery is often considered the primary treatment for craniopharyngiomas, there is a long history of employing RT in the treatment of these tumors. As early as the first half of the 20th century, RT was considered useful in the treatment of craniopharyngiomas.^{100,139} Radiation has been utilized as primary treatment following cyst aspiration, biopsy, or subtotal resection, and as salvage in the setting of recurrent disease. Kramer et al reported a series of 10 consecutive patients treated at the Royal Marsden Hospital, London, England, during the early 1950s with biopsy and cyst decompression followed by radiation.^{101,140} Doses of 55 to 70 Gy (gray) were delivered over 6 to 7 weeks with 2 million-volt roentgen rays. At 5 to 15 years of follow-up, three of the adult patients had died of unrelated causes. The remaining adults and the six children were alive without sign of recurrence, and all were considered to be “functioning well.”

Subtotal resection alone results in progression rates of 55 to 85%, as assessed in several retrospective series.^{16,59,101,141,142} Progression often occurs early in this setting, within months to a few years after subtotal resection.^{5,101} The addition of postoperative RT in the setting of gross residual disease can decrease that recurrence rate to 15 to 20% (▶ Table 37.5). Although no Phase III data exist for a direct comparison of

Table 37.5 Recurrence rates following subtotal resection alone and subtotal resection plus radiotherapy

Series	Years of study	Subtotal resection	Subtotal resection + RT
UCSF ²⁰⁹	1956–1972	5/9 (55%)	2/10 (20%)
University of Iowa ⁵⁹	1961–1986	17/20 (85%)	0/8 (0%)
CHOP ¹⁰¹	1974–2001	7/9 (78%)	3/18 (16%)
St. Jude ⁵²	1984–2001	6/7 (86%)	2/15 (13%)

Abbreviations: CHOP, Children's Hospital of Philadelphia; RT, radiotherapy; UCSF, University of California, San Francisco.

subtotal resection alone versus subtotal resection followed by RT, the abundant retrospective data, although imperfect, demonstrate improved local control with the addition of RT following the subtotal resection of tumor.

RT has also been shown to be efficacious in the setting of recurrent disease. Relatively modern series show effective salvage of patients with recurrent disease,^{52,55,101,143,144} and it appears that the use of RT at the time of recurrence or progression yields local control rates similar to those achieved when RT is used in the early (1 to 3 months) postoperative period (▶ Table 37.6). Furthermore, overall survival remains high (85 to 100%) in the salvaged groups.

Given the ability of RT to effectively salvage recurrence and maintain high overall survival rates, the argument could be made to postpone RT until the time of recurrence. However, given a median time to progression of only 12 months in patients with subtotal resection,¹⁴² there may not be much advantage gained with this approach except in young children, who may

Table 37.6 Outcome based on the time of delivery of radiotherapy

Series	Years	Early (No. of patients)	Delayed (No. of patients)
JCRT ⁵⁵	1970–1990	82% local control (37)	83% local control (6)
CHOP ¹⁰¹	1974–2001	84% local control (18)	83% local control (22)
St. Jude ⁵²	1984–2001	86% local control (15)	87% local control (8)
Christie Hospital ¹⁴³	1976–2002	79% 10-year PFS (42)	77% 10-year PFS (44)
University of Seoul ¹⁴⁴	1985–2002	91.2% 10-year PFS (25)	91.3% 10-year PFS (25)

Abbreviations: CHOP, Children's Hospital of Philadelphia; JCRT, Joint Center for Radiation Therapy at Harvard Medical School; PFS, progression-free survival

benefit from a delay that allows further brain development. These children should be followed closely with MR imaging and treated with irradiation at the first sign of radiographic progression.

Dose and Volume

It is not clear if there is a dose–response relationship for craniopharyngiomas. Three series have noted a dose response for local control with doses higher than 54 to 60 Gy.^{56,145,146} However, the vast majority of series in the literature do not report a dose response,^{59,147} and the reported high local control rates have been achieved with doses of 54 to 55.8 Gy.^{52,55,101} Given the potential increased risks for optic neuropathy and necrosis with doses of 60 Gy or more, most radiation oncologists use 54 to 55.8 Gy (in daily fractions of 1.8 Gy) in the treatment of craniopharyngiomas.

Treatment planning for RT relies on the accurate delineation of tumor on CT and MR imaging. The volume of RT is defined as the tumor with a margin. It is important to include the full extent of the cystic components of the tumor in the treatment volume. If cysts have been drained, the target volume should be based on the decompressed volume, including the full extent of the cyst wall. Thus, the gross tumor volume usually includes any radiographically identified enhancing or nonenhancing tumor and cyst/cyst wall. This classically has been expanded by 10 mm to create a clinical target volume; however, some authors have suggested that with highly conformal techniques, tight immobilization, and real-time imaging, the clinical target volume margins might even be decreased to 5 mm,¹⁴⁸ and most radiation oncologists favor the smaller expansions. An additional 3 to 5 mm is added to the clinical target volume to create a planning target volume.

As planning target volumes have become increasingly conformal, the importance of monitoring for cyst expansion and adaptive planning needs to be emphasized. It has been reported that 35 to 60% of patients may manifest an increase in the target volume during irradiation,^{148,149} and the increase in planning target volume on average is 11%.¹⁴⁸ In the early experience with conformal RT for craniopharyngiomas at St. Jude Children's Research Hospital, however, few patients required a change in treatment planning despite the change in volume during irradiation, primarily because relatively “large” clinical target volume and planning target volume margins of 10 mm and 3 to 5 mm, respectively, were used. As margins have become “tighter,” serial imaging during therapy should be considered

to ensure that there is no re-expansion of cysts that would require altering the target volume and/or adjusting the treatment plan. Unfortunately, it is still unclear how to identify patients who are at risk for tumor expansion during RT, and the best method for imaging during RT has not yet been defined.

Techniques of External Beam Radiation

A variety of techniques have been employed in the treatment of craniopharyngiomas. In the 1950s and 1960s, treatment was delivered with cobalt 60, usually through lateral parallel opposed portals. This meant that both temporal lobes received higher doses than did the tumor. The advent of linear accelerators changed the way radiation was delivered, allowing a “third” field or “arc rotation” such that the doses to the surrounding normal brain could be decreased. The advent of CT and MR imaging has allowed improved definition of tumor volumes and normal structures at risk, and increasingly sophisticated computer software has advanced treatment planning and delivery.

Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy

A typical three-dimensional conformal RT plan might employ five fields to deliver the full dose to the target volume while limiting the dose to the surrounding brain to 30 to 40% of the target volume dose (► Fig. 37.3). Published data support the idea that treating conformally to small volumes results in outcomes equivalent to those achieved with conventionally planned RT. Merchant et al showed in a Phase II trial of conformal RT that the irradiated volume for craniopharyngioma could be safely reduced without compromising tumor control.¹⁵⁰ Doses of 54 to 55.8 Gy were administered to the gross tumor volume (solid and cystic components), and a 10-mm margin was added to create a clinical target volume. The estimated 3-year progression-free survival rate was 90%.

Intensity-modulated RT is a form of three-dimensional photon irradiation that utilizes “beamlets” (i.e., beams of different radiation intensity) to deliver irradiation through multiple fields. Intensity-modulated RT plans can be highly conformal and sculpt the dose around critical structures; however, this is achieved usually at the price of increased integral doses (i.e., low doses spread out over large areas) (► Fig. 37.4).

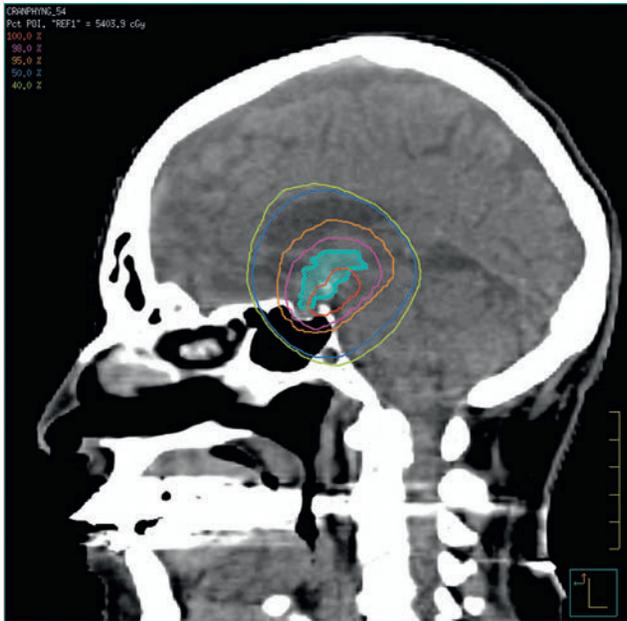


Fig. 37.3 Three-dimensional conformal radiation therapy treatment plan.

Stereotactic Radiosurgery

Stereotactic radiosurgery (the delivery of a single fraction of radiation with a nonrelocatable head frame) with either CT/MR fusion- or MR-guided planning allows submillimeter accuracy of treatment and dramatic sparing of the frontal and temporal lobes. Early publications of stereotactic radiosurgery for craniopharyngiomas reported local control rates of 78 to 100% with a median follow-up of 1 to 5 years.^{151–154} More recently, with longer follow-up, the local control rate has been reported to be on the order of 65 to 85%.^{155,156} As shown in a series from the University of Pittsburgh, complete radiosurgical coverage of the tumor and a peripheral dose of 12 to 13 Gy appear to be associated with better tumor control.¹⁵⁶ Despite its excellent ability to limit the dose to normal brain tissue, stereotactic radiosurgery has limitations in the treatment of craniopharyngioma. This technique requires the precise radiographic delineation of a target generally smaller than 3 cm; in the postoperative setting, it is frequently difficult to differentiate tumor from postoperative changes, and thus, a potential pitfall is the inadequate coverage of residual microscopic disease. Furthermore, this technique frequently is contraindicated because of tumor proximity to adjacent optic structures, which typically are limited to approximately 8 Gy.¹⁵⁷ Therefore, tumors that are not at least 5 mm away from these structures are not suitable for treatment with a single fraction and must be treated with a fractionated technique.

Fractionated Stereotactic Radiotherapy

A technique that allows fractionation and targeting of the entire area at risk, while still markedly limiting the dose to surrounding brain, is fractionated stereotactic RT. Tumors that are adjacent to or involve the optic structures can be treated in this fashion by exploiting the radiobiological advantage of fractiona-

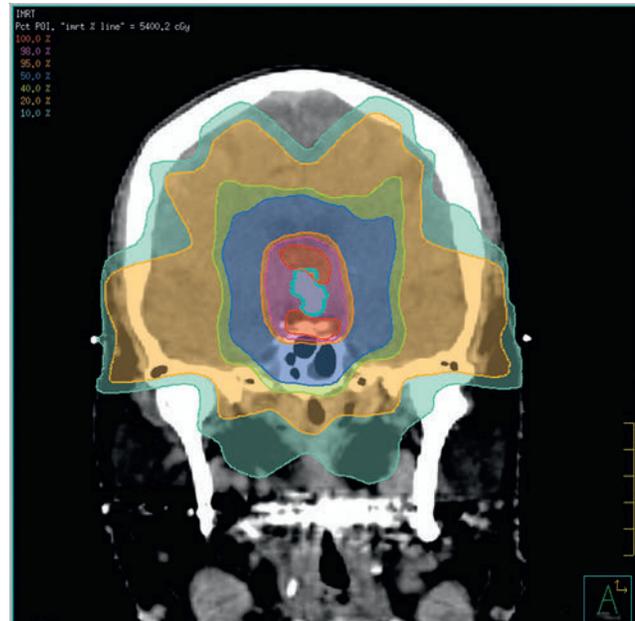


Fig. 37.4 Intensity-modulated radiation therapy treatment plan.

tion. This technique requires rigid immobilization with a relocatable head frame. Treatment is delivered on a daily basis with conventional fractionation schedules. Tarbell et al reported the feasibility of fractionated stereotactic RT in the treatment of craniopharyngioma early in the development of this technique.^{158–160} A series from the University of Heidelberg reporting on the use of fractionated stereotactic RT for craniopharyngiomas noted 100% local control at 10 years in 26 patients who were treated with a median dose of 52.2 Gy.¹⁶¹ No statistical differences have been reported in terms of tumor control with fractionated stereotactic RT between children and adult patients, and reduced toxicity has been reported with fractionated stereotactic RT.^{162–164} Overall, fractionated stereotactic RT is a suitable treatment technique for many craniopharyngiomas, and its efficacy is comparable to that of conventional RT, with control rates on the order of 90%.¹⁶⁵

Protons

Given the long survival of patients with craniopharyngiomas, efforts continue to be directed at reducing the long-term morbidity associated with radiation by further refining the delivery of RT. Protons are a means to do this, and their use in the treatment of craniopharyngiomas goes back several decades. The physical characteristics of protons make possible the delivery of targeted doses of irradiation with integral doses lower than those associated with intensity-modulated RT. The initial Harvard experience combining protons with photons in 5 children with craniopharyngiomas reported 100% tumor control at a median follow-up of 13 years; only 1 child exhibited "learning difficulties and slight retardation."¹⁶⁴ In a series from Loma Linda with 5 years of follow-up, tumor control was higher than 90%.¹⁶⁶ Among the 12 patients who survived, Nine children experienced no new toxicities, one child developed panhypopituitarism at 36 months, another experienced a cerebrovascular

accident at 34 months, and a third patient (who had received a course of photon RT before protons as part of the initial treatment) developed a posterior fossa meningioma nearly 5 years after the protons.

Late Effects of Radiation Therapy

The long-term sequelae of irradiation include endocrinopathies, optic neuropathy, radionecrosis, vascular injury including the development of moyamoya disease, and secondary tumors. Hypopituitarism is the main long-term complication of RT; fortunately, optic neuropathy, brain necrosis, and second malignancy are uncommon.

Pituitary abnormalities are among the most common morbidities after treatment. Although about 25% of patients manifest a hormonal abnormality before treatment, the vast majority ultimately develop some loss of pituitary function after treatment. From 79 to 97% of patients will be thyroid-deficient, and 58 to 93% of patients will be growth hormone-deficient regardless of what treatment is employed.^{52,56} Although the incidence of diabetes insipidus appears higher in patients treated with radical surgery (79 to 88%) than in those treated with RT and limited surgery (22 to 38%),^{55,101} the frequency of abnormal gonadotropin-releasing hormone secretion is lower in patients treated with surgery (27%) than in those who receive combined-modality treatment (53%).⁵²

Visual impairment due to optic nerve or chiasm damage from RT is on the order of 1 to 1.5% when doses of 55 Gy or lower are delivered with conventional fractionation, but the rate increases with higher doses.^{146,147} Radionecrosis, like optic damage, also depends on the total dose and fractionation schedules; fortunately, it is rarely encountered in the treatment of craniopharyngiomas. However, when doses of 60 Gy have been used, an incidence of 12.5% has been reported.¹⁶⁷ Late vascular events, particularly moyamoya syndrome, have been recognized in the irradiation of sellar and parasellar tumors. The incidence appears to be 2 to 4% in the treatment of craniopharyngiomas.^{55,146}

Although neurocognitive dysfunction may result from irradiation, focused techniques may lessen the impact of this sequela. Interestingly, studies that have compared neurocognitive function after radical surgery with that after limited surgery plus postoperative RT generally either favor the latter or show no difference.^{2,16,55,168} A series from St. Jude Children's Research Hospital that evaluated neuropsychometric data in patients who had been treated with surgery alone or with limited surgery plus RT showed a decrease in the mean full-scale IQ, verbal IQ, and performance IQ for the group as a whole, but there was no statistical difference between the two groups in any of these measurements.⁵² Furthermore, it appears that neurocognitive toxicity may be mostly related to surgical morbidity and, not surprisingly, to the dose of RT to particular volumes of the brain.¹⁵⁰ In another series from St. Jude Children's Research Hospital, 28 pediatric patients (median age, 7 years) treated between 1997 and 2003 with conformal RT for craniopharyngioma were evaluated serially with neuropsychometric testing. In addition to surgical morbidity, cognitive outcome as measured by longitudinal IQ was adversely affected by the percentage of total brain, supratentorial brain, or left temporal lobe volume receiving a dose in excess of 45 Gy.

Second malignancies are a long-term complication that occur following RT and offer a compelling argument against the indiscriminate use of RT in all cases of childhood craniopharyngioma. Their identification requires extended follow-up.^{55,166} Although the development of a lethal secondary malignancy in children with primary central nervous system tumors is relatively rare,¹⁶⁹ its occurrence following the treatment of a benign tumor is a devastating event. In general, cranial irradiation is associated with a higher risk for carcinogenesis at younger ages and should be employed judiciously in young children with benign tumors.

The modeling of photon and proton plans for the treatment of craniopharyngioma suggest that the increasing use of protons for pediatric craniopharyngioma may decrease long-term toxicity.¹⁷⁰ Retrospective target planning analyses in pediatric patients with craniopharyngiomas have shown that protons result in statistically lower doses to the cochlea, optic chiasm, hippocampus, dentate gyrus, subventricular zone, blood vessels, and brain.^{148,171} Furthermore, a threefold difference between the integral dose values for intensity-modulated RT and those for double-scatter proton therapy was identified, a finding that has implications for decreasing the risk for second malignancies in these children.

37.5.3 Intracavitary Therapy

The indications for intracavitary therapy and the choice of agents (radionuclide or bleomycin) are still in a process of evolution. Both tumor and patient characteristics should be considered before intracystic therapy is administered: the feasibility of radical resection, including the availability of surgical expertise and postoperative endocrinologic support; the suitability of partial resection and irradiation as treatment for the tumor; the size, location(s), and number of cysts; whether the tumor is primary or recurrent; and the clinical condition and age of the patient.¹⁷² Intracavitary therapy is most effective and often curative in primary monocystic tumors with relatively thin walls, although significant control of the cystic components of recurrent tumors can be achieved.¹⁷²⁻¹⁷⁹

Aspiration

Simple stereotactic aspiration of tumor cysts or placement of an Ommaya reservoir into the cyst for serial aspirations is never indicated as primary therapy in children and should be reserved for palliation when all other treatment modalities have failed.^{89,175,180} Frequent aspiration tends to stimulate cyst fluid production, leading to progressively shorter symptom-free intervals. Solid tumor growth is unimpeded and may extend into areas of decompressed cysts. Aspiration may be required to control cyst volume pending the therapeutic effect of intracavitary irradiation (vide infra).

Intracavitary Irradiation

Local treatment of cystic craniopharyngioma with intracavitary beta irradiation was first described 60 years ago by Leksell and Liden.¹⁸¹ The ideal agents are colloidal suspensions of beta-emitting radionuclides that are evenly distributed along the walls of cystic tumors, have tissue half-lives that allow an

adequate but not excessive dose, and have a rapid falloff in tissue penetrance to avoid corollary radiation injury to adjacent neural tissue. Clinical experience has established yttrium 90 and phosphorus 32 as the preferable radioactive isotopes, with an ideal dose of 200 to 250 Gy to the cyst wall.^{172,175,176,182} There has been controversy over the relative efficacy and safety of ⁹⁰Y compared with ³²P.^{172,173,175-177,182} In part, this happened because access to ⁹⁰Y was limited to Great Britain, Europe, and Japan. Contemporary reports show similar cyst response rates to both of these radionuclides, with the diminution or obliteration of cysts reported in 74 to 100% of cases.^{173,175-177,183-185} ³²P is currently the preferred agent, with its shorter tissue penetration and longer half-life offering the possibility of diminished injury to adjacent structures, especially the visual pathways and hypothalamus.¹⁷⁵⁻¹⁷⁷

Radionuclide is administered by stereotactic cannulation of the cyst, usually through a precoronal trajectory, with a fine needle. The use of an indwelling catheter connected to an Ommaya reservoir has been abandoned by most centers because the catheters have distal holes that may be located outside the cyst.^{175,177} Leakage of radionuclide has been reported in 10 to 22% of patients, although clinical sequelae have been rare.^{175-177,183-187}

Cyst regression after intracavitary irradiation occurs gradually over several months. Large, symptomatic cysts often require subsequent puncture and drainage during this period of involution. Durable control is seen in 80 to 96% of the treated cysts, with a complete response and permanent obliteration seen in 12 to 45% of the cysts.^{173,175-177} Intracystic irradiation does not control solid tumor growth, nor does it prevent the development of new cysts.

Treatment-related mortality is low, below 2%; however, morbidity varies among different series from 6 to 58%.^{172,173,175,188,189} Preoperative optic atrophy, intimate contact of the cyst wall with the optic nerves, previous or concurrent external beam irradiation, and the use of ⁹⁰Y, with its greater tissue half-value, are risk factors for visual deterioration.^{175,177,185} New endocrine deficiencies occur in approximately 10% of the patients; however, treatment-related diabetes insipidus is uncommon.^{176,177} Other neurologic complications and delayed cognitive deficits are rare.

Intracavitary Bleomycin

Bleomycin is an antineoplastic antibiotic that interferes with DNA production and has demonstrated clinical efficacy in squamous cell carcinomas.¹⁹⁰ The cell cycle kinetics and spatial distribution of S-phase proliferative cells in the squamous epithelium of craniopharyngioma cysts provide a rationale for the use of antineoplastic agents.¹⁹¹ An Ommaya catheter is placed into the cyst either stereotactically or at craniotomy. Several days after catheter placement, a contrast injection and CT are performed to verify that there is no leakage of cyst contents. A 1.5- to 10-mg dose of bleomycin is injected at 1- to 2-day intervals, depending on the cyst volume. Injections are repeated over a 10- to 21-day period for an average total dose of 60 to

80 mg.^{179,192} Although most centers have measured cyst fluid lactate dehydrogenase, no consistent pattern has emerged to guide therapy.¹⁷⁸ The major risk is leakage of bleomycin into the subarachnoid space or ventricles, with ensuing ventriculitis, meningitis, or vasospasm. To date, this has been reported only anecdotally (Sainte-Rose, personal communication, 1997). Visual deterioration and new hearing deficits have been noted in individual patients.^{178,192}

As with intracystic irradiation, involution of cysts occurs slowly over several months. Although the total number of patients treated remains small, the reported series demonstrate reduction in cyst volume in almost all patients, with up to 50% of patients showing complete disappearance of the cyst and indefinite remission.^{37,178,179,192,193} Bleomycin may also be used as a surgical adjunct to decrease the technical difficulty of subsequent surgical resection, particularly in patients with mixed solid and cystic craniopharyngiomas. Intracavitary therapy will produce a thick, tough cyst wall that is resistant to tearing and is easier to maintain intact, dissect, and remove en masse than the more common fragile, diaphanous cyst tissue. In contrast to other treatment modalities, bleomycin does not induce arachnoidal scarring or damage the gliotic plane between the tumor and normal hypothalamus that is crucial for safe resection.

Intracavitary Interferon

Interferon- α has been used as both systemic^{194,195} and intracavitary¹⁹⁶ therapy for primary craniopharyngiomas. Cavalheiro et al recently reported an international multi-institutional open-label trial of intracavitary interferon- α in 60 children.¹⁹⁶ Short-term disease control, defined as a decrease of more than 50% in tumor volume, was obtained in 78% of the patients. New endocrine deficiencies developed in 13%, and 30% had mild side effects. Interestingly, three of the responders had previously experienced tumor progression after bleomycin, but salvage was achieved with interferon. There was no information on long-term outcome or durability of disease control.

37.5.4 Treatment of Recurrent Craniopharyngiomas

Not every recurrent craniopharyngioma should be treated. The age of the patient, location of the tumor, nature of the previous therapy, and severity of the symptoms and signs should be thoroughly assessed before treatment is undertaken. Although neither prior surgery nor irradiation precludes the possibility of a curative resection in recurrent tumors, many surgeons have reported increased morbidity, mortality, and failure to obtain a total tumor removal compared with surgery in primary tumors.^{9,89,113,197,198}

Reoperation can be curative, especially with solid tumors.^{9,37} The nature and extent of treatment of the primary tumor influence the likelihood of curative resection at recurrence. Previous radical surgery may render further resection hazardous or even impossible. In primary tumors, there is always a dense gliotic

reaction separating the tumor from the normal neural tissue of the hypothalamus.^{29,89,198} This gliotic reaction, which forms a natural cleavage plane between tumor and hypothalamus, is probably destroyed by previous radical surgery. The increased incidence of visual, neurologic, and neuropsychological deficits accompanying surgery for recurrence may be partially related to direct hypothalamic and optic pathway injury due to the lack of this reactive glial barrier.¹⁹⁹

Because both tumor and cicatrix from previous surgery may extend diffusely throughout the suprasellar cisterns, displacing and distorting normal structures, identification of the normal vascular anatomy provides essential landmarks. The extended pterional approach with removal of the supraorbital rim and zygomatic process of the frontal bone and a wide sylvian dissection may provide a clean plane of dissection free from arachnoidal scarring and adhesions, particularly in patients who have had a previous subfrontal resection. The violation of arachnoidal planes during an aggressive primary resection may promote a dense mesenchymal reaction from the arterial adventitia to recurrent tumor, precluding the development of a safe plane of dissection and total removal. Calcific tumor is particularly likely to adhere to major vessels. Excessive, imprudent manipulation may result in carotid or basilar laceration and significant morbidity.^{60,73,199}

Recurrent tumor limited to the sella turcica is best removed through a transsphenoidal approach.⁸⁴ Careful consideration of the anatomical features, meticulous surgical technique, and extensive experience with transsphenoidal surgery are essential for success. Significant suprasellar tumor is a relative contraindication to this approach; however, transsphenoidal cyst drainage for palliation may occasionally be appropriate.

Since 1985, 43 patients have undergone an attempted total resection of recurrent craniopharyngioma; a gross total resection was obtained in 68%, compared with complete resection in 100% of primary tumors.⁶² Tomita and McLone⁶⁰ reported total resection in 55% of recurrent tumors versus 79% in primary operations. Most of these patients had a second recurrence that required further surgery and irradiation for tumor control. Hoffman et al¹² reoperated on 16 of 17 recurrent tumors and achieved a radical resection in only 5 patients. Of the 17 patients, 47% experienced a second recurrence. Yasargil et al⁹ reported 32 radical resections (19 children and 13 adults) for recurrent tumors among 144 cases; total resection was obtained in 56.3%.

In the senior author's series, 1 operative death, 2 late treatment-related deaths, and 2 deaths from tumor progression occurred, for a case mortality rate of 20%. One patient died of a radiation-induced glioblastoma 8 years after gross total removal of recurrent tumor and postoperative. Matson and Crigler⁶ had 5 postoperative deaths among 14 reoperations. Sweet¹⁹⁹ was supportive of reoperation following a less extensive primary procedure but cautions against aggressive surgery for recurrence if the patient has had previous radical surgery. All 5 of his patients with previous radical surgery died within 6 months of attempted reoperation for recurrence. In a

multicenter international study,³⁷ there was a 3.7% surgical mortality rate for primary surgery and a 13% operative mortality rate after secondary radical surgery.

Yasargil et al⁹ did not experience an increase in operative mortality; however, the long-term survival was 59.4% after secondary microsurgery, compared with 90% after operation for primary tumors. Both children and adults fared poorly, with 42.1% and 38.5% mortality rates, respectively. Yasargil comments that the difference in outcome could "largely be attributed to the difficulty in dissection at second or subsequent operation."

37.6 Quality of Life

The impact of radical resection versus limited surgery with irradiation on neuropsychological functioning and quality of life is controversial.^{2,12,23,43,200-204} In an evaluation of the psychosocial sequelae of craniopharyngiomas, regardless of treatment modality, it is critical to consider these children as having a chronic disease, requiring indefinite medical supervision for their hormone replacement therapy and periodic imaging to monitor for tumor recurrence. Children who have chronic illnesses demonstrate more psychological symptoms than normal children but fewer symptoms than patients who have overt psychological disorders, with internalizing disorders more common than behavioral problems.²⁰⁵ The entire family unit is stressed by the need for ongoing medical care, the coordination of multiple physician appointments, and the uncertainty surrounding each MR imaging session.

Isolated results on neuropsychological testing may not predict psychosocial or academic performance. Mild deficits in recent memory may not impair normal educational advancement if intelligence is adequate.¹² Merchant et al described the late effects arising from the treatment of 30 patients, half of whom were initially treated with surgery and the remaining half with limited surgery and irradiation at the St. Jude Children's Research Hospital.⁵² Results from multiple administrations of a variety of IQ measures at the time of initial evaluation and serially in 23 patients noted a decrease in IQ for the entire group but found no statistically significant difference between the two treatment groups. Additionally, 29 patients completed an abbreviated health status classification questionnaire, which indicated impairments for 23 (79%) of the group involving (in order of frequency) emotion, pain, sensation, mobility, and cognition; however, there was no statistically significant difference between the two treatment groups. Despite the lack of significant findings between the two different treatment groups, it is clear that both treatment modalities can yield notable deficits.

Riva et al²⁰⁶ evaluated the late effects of radical surgery alone for craniopharyngioma with neuropsychological and personality measures. The authors did not note any neurologic (with the exception of visual dysfunction), cognitive, or short-term memory deficits in this cohort. The study did describe the most frequent behavioral disorder as the inability to withstand frustration, followed by unmotivated fits of anger, emotional lability, and cognitive inflexibility. These symptoms can be best

understood as presumed effects on the frontal lobes arising from the surgical approach; the frontal lobes mediate aspects of impulsivity and cognitive flexibility to the hypothalamus, which plays an integral role in affect regulation. Some of the deficits associated with the impairment of frontal lobe function may be avoided by using the pterional approach, which inherently involves less retraction on the frontal lobes.

Twenty-nine children treated by the senior author with gross total resection for primary and recurrent craniopharyngioma were evaluated for quality of life and psychosocial function 4 to 17 years after surgery.²⁰⁷ Their overall psychosocial quality of life and their social-emotional and behavioral functioning for externalizing problems were within normal limits. Similar to children with other chronic diseases, they had a borderline significance range for internalizing problems. Recurrent tumors and additional surgery were associated with a decrease in physical functioning and quality of life, whereas a retrochiasmatic tumor location was moderately associated with a lowered psychosocial quality of life and with poorer social-emotional and behavioral functioning. Patients also tended to exhibit global improvement as postoperative time increased.

Retrochiasmatic tumors are more likely to involve the hypothalamus, third ventricle, and limbic system. Evidence of preoperative hypothalamic dysfunction and tumor size may predict those children at risk for postoperative intellectual and behavioral difficulties.⁷⁹ Children with retrochiasmatic tumors will be at greater risk for postoperative weight gain. These children may subsequently limit their activities, causing further anxiety and psychological stress.²⁰⁷

Many of the reports describing poor neuropsychological outcomes are from institutions having limited experience with radical microsurgical resection, multiple surgeons caring for a relatively small number of patients, or a dedicated philosophy of limited surgery and irradiation.^{2,43,57,79} In contrast, at centers with a large volume of radical surgeries and a dedicated neurosurgeon, a good outcome with normal psychosocial integration and age-appropriate academic performance is reported in over 70% of children.^{9,12,23,54,57,60,207}

37.7 Summary

In experienced centers with appropriate surgical expertise, experienced radiation oncologists, endocrinologic support, and socioeconomic resources, the curative treatment of craniopharyngiomas can be achieved in 70 to 90% of children, with maintenance of a good quality of life in more than 90%. Total surgical resection and partial resection with adjuvant irradiation have similar rates of long-term disease control, although with different immediate and long-term sequelae. Small intrasellar tumors are best treated by a transsphenoidal/transnasal route; the indications and long-term outcome for larger tumors approached transsphenoidally are evolving. Intracystic therapy may be appropriate for monocystic tumors without a solid component. Recurrent tumors are problematic; a multimodality approach should be considered, often with a combination of surgery, irradiation, and intracystic therapy to salvage the majority of these patients.

Pearls

- Both partial resection with radiation and radical resection carry similar rates of durable disease control in patients with newly diagnosed craniopharyngiomas when treatment is carried out in centers that have significant experience.
- Morbidity and long-term side effects tend to be acute after surgery and delayed with irradiation. Radical surgery carries a higher rate of endocrine deficiencies, particularly diabetes insipidus, whereas irradiation may cause length vasculopathy and the induction of secondary tumors.
- Radical surgery requires appropriate social and economic support for the long-term management of diabetes insipidus. It may not be an option where health care systems are limited or families are unable to manage the children's medications.
- Transnasal/transsphenoidal resection may be optimal for intrasellar and subdiaphragmatic tumors; however, there is a steep learning curve, particularly when the surgery is performed in young children without pneumatized sphenoid sinuses and large tumors.
- Regardless of treatment, craniopharyngioma is a chronic disease that requires lifelong attention from specialists in neurosurgery, endocrinology, and often psychology.

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38 Pediatric Pituitary Adenomas

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Although relatively uncommon, pituitary adenomas account for 2 to 6% of pediatric brain tumors.¹ Of all pituitary tumors, only 3.5 to 8.5% are diagnosed by the age of 20, and only 25% of those present before the age of 12 (primarily corticotropinomas).² Adenomas that secrete adrenocorticotropic hormone (ACTH) and growth hormone (GH) are the most common type of adenomas in prepubertal children. Prolactinomas predominate in the pubertal and postpubertal populations.³⁻⁷ Prolactin-secreting tumors account for 30 to 50% of pediatric cases, and ACTH-secreting tumors also account for 30 to 50% of pediatric cases. GH-secreting tumors comprise 10% in most series and are the most common type occurring in infants.^{3,6,8} Although nonfunctioning adenomas account for approximately one-third of adult adenomas, they constitute only 5% of pediatric adenomas.^{3,9,10} Thyrotroph- and gonadotroph-secreting adenomas are extremely rare and have been reported in only a few cases. Although they are often sporadic, they can occur in the context of multiple endocrine neoplasia type 1 (MEN-1), McCune-Albright syndrome, Carney complex, or familial isolated pituitary adenomas (FIPAs).¹¹

38.1 Indications for Treatment: Medical and Surgical

Presenting signs and symptoms are generally related to endocrine dysfunction rather than to ophthalmologic complaints but vary according to maturity of the patient. Prepubertal children and pubescent boys typically present with headaches, visual complaints, and growth delay. Pubescent girls present with pubertal arrest and hypogonadism with or without galactorrhea. Fortunately, pituitary apoplexy is a rare event in patients with pituitary adenomas, and surgical emergencies are therefore uncommon in the pediatric population.¹²⁻¹⁴ Neurosurgical emergencies include increased intracranial pressure and rapid visual deterioration that may require emergent drainage of the ventricles (in the case of hydrocephalus) or cyst contents in order to stabilize the patient.

The evaluation of a pituitary mass includes contrast-enhanced magnetic resonance (MR) imaging with dedicated pituitary imaging, a full biochemical evaluation of the hypothalamic-pituitary axis, and an ophthalmologic evaluation (see box "Preoperative Evaluation of a Pituitary Adenoma (p.503)"). Computed tomography (CT) may also be helpful to assess the bony architecture and degree of pneumatization of the sphenoid sinus. CT may also help in the differential diagnosis of pituitary adenoma versus a craniopharyngioma. Stress-dose corticosteroids should be considered for any patient with a large pituitary mass who is experiencing physiologic stress.

Preoperative Evaluation of a Pituitary Adenoma

- Imaging
 - Magnetic resonance imaging + gadolinium with pituitary sequences
 - Computed tomography for bony architecture
- Vision
 - Formal neuro-ophthalmologic examination
 - Visual fields
- Endocrine
 - Adrenocorticotropic hormone (ACTH)
 - Cortisol (a.m.)
 - Follicle-stimulating hormone (FSH)
 - Luteinizing hormone (LH)
 - Growth hormone (GH), insulin-like growth factor-1 (IGF-1)
 - Prolactin
 - Thyroid-stimulating hormone (TSH), free thyroxine (T₄)
 - Basic metabolic panel
 - Urine specific gravity and sodium

Source: Adapted from Kiehna EN, Payne SC, Jane JA Jr. Surgical treatment of Rathke's cleft cysts. In: Laws ER Jr, Sheehan JP, eds. *Sellar and Parasellar Tumors*. New York, NY: Thieme Medical Publishers; 2011:chap 10.

38.1.1 Prolactinomas

Prolactinomas are the most common pituitary tumor, comprising nearly 50% of pituitary tumors in children. They generally present at the time of or after puberty with primary or secondary amenorrhea in girls.¹⁵⁻¹⁷ Males more frequently have macroprolactinomas, which are associated with a higher incidence of neurologic and ophthalmologic signs.¹¹ The diagnosis is confirmed by measuring the serum prolactin, with values greater than 200 ng/mL diagnostic of a prolactinoma.

Medical therapy is the mainstay of treatment for these tumors. Prolactinomas should first be treated with dopamine agonists (e.g., bromocriptine, cabergoline), which are effective in normalizing the PRL levels and shrinking the tumor mass in the majority of children and adolescents (► Fig. 38.1).^{3,16,18} Cabergoline is often favored over bromocriptine because it has a longer half-life and can be administered on a weekly basis to normalize the serum prolactin levels and restore gonadal function. It has also proved to be more effective in patients whose tumors are poorly responsive or resistant to other agents.¹⁸⁻²⁴ If patients cannot tolerate the medications or if their tumors

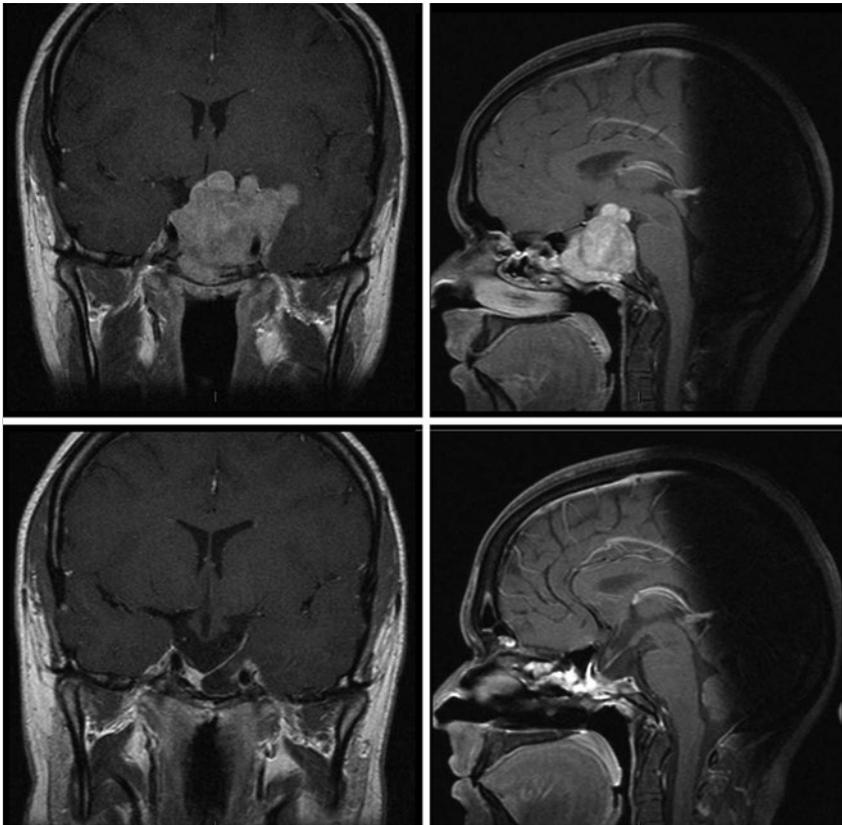


Fig. 38.1 Prolactinoma before (above) and 3 weeks after (below) medical treatment with cabergoline. Vision returned to normal within 1 week of the initiation of medical therapy.

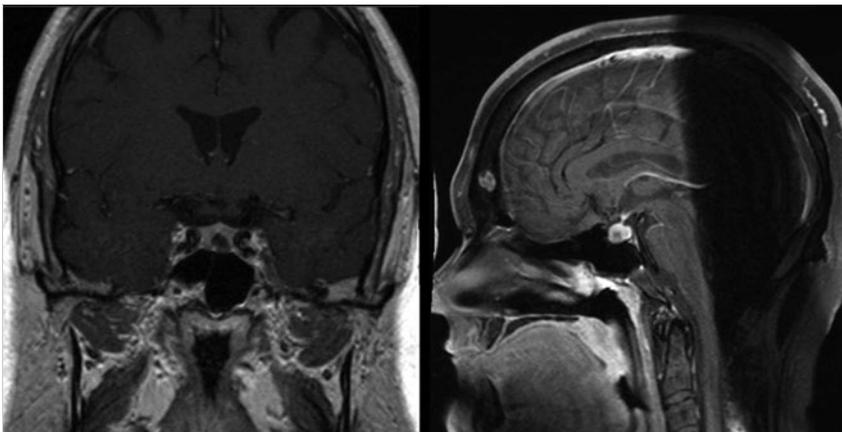


Fig. 38.2 Corticotropinoma. Coronal and sagittal T1-weighted gadolinium-enhanced images revealing a left-sided intrasellar adenoma.

are refractory to the medications, surgical remission may be obtained in 85% of patients with microprolactinomas. Lower rates of remission are expected in those with macroadenomas and those with tumors invading the cavernous sinus. However, surgical debulking may reduce the tumor burden enough to allow either radiosurgery or the recapture of effective medical therapy.

38.1.2 Corticotropinomas

Corticotropinomas (Cushing disease) typically appear in prepubescent children between 11 and 15 years of age and are a frequent cause of adrenal hyperfunction in this age group.^{25–27}

Weight gain is the common hallmark; this is accompanied by growth failure; premature puberty; facial plethora; atrophic striae in the abdomen, legs, and arms; muscular weakness; hypertension; and osteoporosis. Children may also have impaired carbohydrate tolerance (although frank diabetes mellitus is uncommon). Increases in adrenal androgens may cause acne and excessive hair growth. Corticotropinomas are diagnosed through the measurement of basal and stimulated levels of cortisol and ACTH (► Fig. 38.2).

Cushing syndrome must first be confirmed on the basis of serially elevated 24-hour urinary free cortisol (corrected for the child's body surface area) or 11 p.m. salivary cortisol measurements. Administration of low dose of dexamethasone at

midnight (15 µg/kg) does not induce suppression of morning serum cortisol concentrations in patients with Cushing syndrome. Cushing disease must then be distinguished from ectopic ACTH-producing lesions. Suppression of cortisol by more than 50% after the administration of high-dose dexamethasone at midnight (120 µg/kg) will confirm that hypercortisolism is due to an ACTH-secreting pituitary adenoma.²⁸ In many cases in which neuroimaging is not diagnostic, inferior petrosal sinus sampling can have a high specificity both for diagnosing a pituitary location with ACTH production (sensitivity of 97%) and defining laterality (in 75% of cases), but it carries a high rate of false-positive results.

Cushing disease is preferentially treated by transsphenoidal resection; this results in a surgical remission in the majority of children, with initial remission rates of 70 to 98% and long-term remission rates of 50 to 98% with multimodal therapy.^{1,3,8,25,26,29-33}

38.1.3 Somatotropinomas

Somatotropinomas (acromegaly) are rare in children (5 to 15% of pituitary tumors) but are notable for causing gigantism before growth plate fusion, diabetes, visual disturbances, and/or headaches.³ These tumors may occasionally concomitantly secrete prolactin and thyroid hormone, resulting in additional symptomatology. They may be associated with McCune-Albright syndrome or Carney complex as a result of somatotroph hyperplasia.¹¹ Somatotropinomas are usually diagnosed clinically but are confirmed by measuring circulating concentrations of insulin-like growth factor-1 (IGF-1,) which correlate with the integrated 24-hour GH secretion levels (► Fig. 38.3). Further evaluation includes an oral glucose tolerance test; failure of GH suppression or a paradoxical increase in GH production identifies patients with a GH-secreting pituitary lesion.³⁴

Acromegaly has traditionally been treated primarily with transsphenoidal surgery. In most surgical series, approximately 50 to 70% of patients with acromegaly achieve normal IGF-1 levels.³⁵⁻³⁷ Treatment with somatostatin analogues (e.g., octreotide, lanreotide) has been applied to the adult population, and the growth hormone receptor antagonist pegvisomant has been effectively

used alone or in combination with somatostatin analogues. There is little if any experience in children with these agents.

38.1.4 Thyrotropinomas

Thyrotropinomas are extremely rare but usually present as macroadenomas with mass effect symptoms, such as headache and visual disturbance, together with various symptoms and signs of hyperthyroidism.^{38,39} They are confirmed through thyroid function tests. A failure to respond to a thyroid-releasing hormone (TRH) stimulation test distinguishes a thyrotropinoma from central thyroxine (T₄) resistance. An elevated α -subunit level relative to the thyroid-stimulating hormone (TSH) level may also be useful.^{38,39}

Thyrotropinomas are primarily treated with transsphenoidal resection; however, they often require adjuvant radiation therapy. These tumors may also respond to somatostatin analogues.

38.1.5 Nonsecreting Adenomas

Nonsecreting adenomas are uncommon in childhood because they are slow-growing and often take decades before signs of pituitary insufficiency and mass effect are evident.⁴⁰ Apoplexy is a rare event in the pediatric population and is most common with nonfunctioning macroadenomas (up to 21%). Cystic formation aside from hemorrhage may occur in up to 17%.⁴⁰

38.2 Surgical Treatment

There are certain challenges to transsphenoidal surgery in children, including small nares, narrow passageways, and poor pneumatization of the sphenoid sinus. The sphenoid sinus begins to become pneumatized at about 3 years of age, and pneumatization proceeds rapidly until age 7; the sinus reaches its average normal capacity of 7.5 mL in adolescence. In approximately 5% of patients, the sphenoid bone remains minimally pneumatized (► Fig. 38.4). Because of this lack of pneumatization and the shallowness of a child's sella turcica relative to that of an adult, transsphenoidal approaches in children often

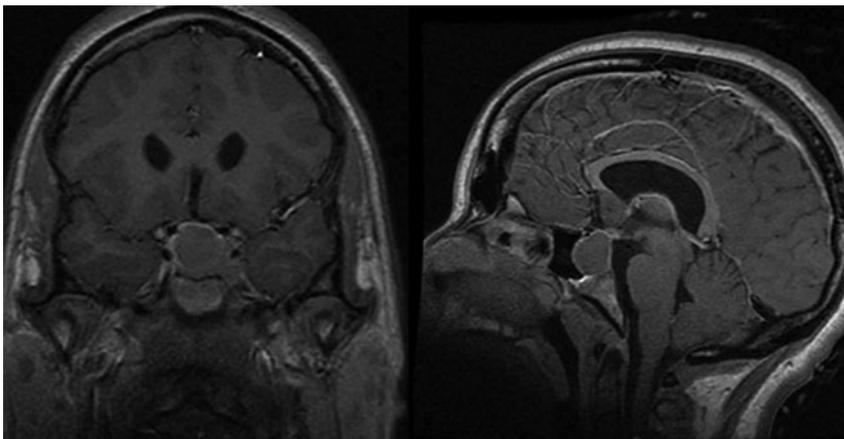


Fig. 38.3 Somatotropinoma. Coronal and sagittal T1-weighted gadolinium-enhanced images revealing a right-sided intrasellar adenoma. Note the frontal bossing and expanded diploic space on the sagittal image.

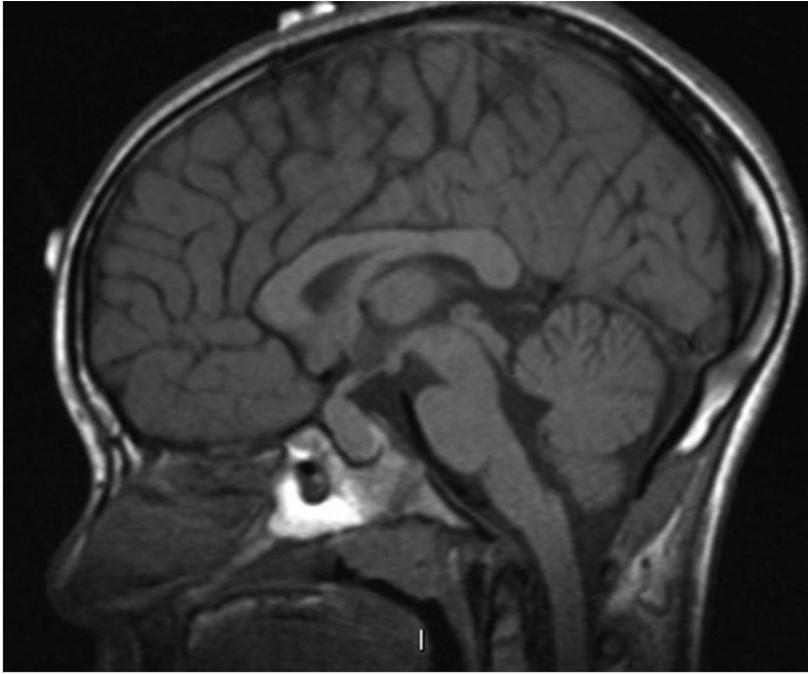


Fig. 38.4 Incomplete pneumatization of the sphenoid sinus in an 8-year-old with a pituitary mass.

require substantial drilling of the sphenoid bone, particularly in the case of microadenomas.

Regardless of the surgical technique used in the transsphenoidal approach (described below), outcomes with the two approaches are generally comparable.^{40–43} Recovery ordinarily is quite rapid following pituitary surgery, and the child often leaves the hospital within a few days and is back at school and engaging in normal activities within 2 to 4 weeks. Long-term follow-up with a specialized team, including a neurosurgeon and an endocrinologist, is crucial for optimal outcomes.

38.2.1 Microscopic Transsphenoidal Approach

Historically, pituitary adenomas were resected through a sublabial transsphenoidal approach, as described by Harvey Cushing.⁴⁴ Resection may be performed via either a sublabial or an endonasal approach. Although the benefits include a three-dimensional view, the surgeon may be limited by a fixed view and smaller field. Adequate exposure is often possible through an endonasal approach, but the sublabial approach may be favored for young children, whose small nares may not allow the unencumbered passage of transsphenoidal instruments.⁴⁵

38.2.2 Endoscopic Transsphenoidal Approach

The endoscopic transsphenoidal technique is used more commonly in adult patients; it is used less frequently in the pediatric population, perhaps because of perceived challenges, including small nostrils, narrow nasal cavities, and poor pneumatization

of the sphenoid sinus. Nevertheless, the advantages of the endoscopic approach are becoming increasingly recognized in the pediatric population.^{29,44,46} In contrast to a microsurgical technique, the endoscopic technique allows a wider field, angled viewpoints, and closer inspection.^{29,47} The approach includes a two-nostril technique, with wide exposure of the sphenoid sinus to maximize the surgeon's working space. In children, poor pneumatization of the sphenoid sinus necessitates a significant amount of drilling, and this is best performed with the use of neuronavigation.

Once the dura is exposed, the MR images should be reviewed and the micro-Doppler ultrasound probe used to assess the intercarotid distance. During the dural opening and tumor dissection, an attempt should be made to preserve the tumor and pituitary pseudocapsule. For pituitary microadenomas, every attempt should be made to preserve the tumor capsule during dissection such that it can be removed, unruptured, in one piece. For pituitary macroadenomas, the goals of surgery are to debulk the tumor and decompress the parasellar structures. When a pseudocapsule cannot be maintained, the following should be removed in a sequential fashion: first the inferior portions of the tumor, then the lateral extensions, and finally the superior portions. Early removal of the superior portions of the tumor will cause early descent of the diaphragm and increase the likelihood of incomplete tumor removal. A common location for residual tumor is at the junction of the cavernous sinus wall and the diaphragm. This location should be carefully inspected before closure.

For tumors with suprasellar extension and a prefixed chiasm, it may be warranted to remove the tuberculum and a portion of the planum sphenoidale to allow an extended transsphenoidal approach, although the increased risk for a postoperative cere-

brospinal fluid (CSF) leak must be kept in mind. When this more extended approach is to be performed and a CSF leak is anticipated preoperatively, a pedicled nasoseptal mucosal flap may be harvested at the beginning of the case to be used for the reconstruction. Otherwise, attempts are made to preserve the nasoseptal artery in the event an unexpected CSF leak is encountered and a “rescue” flap reconstruction may be necessary. The ability to switch between angled endoscopes allows the visual confirmation of complete removal of the adenoma and/or cyst contents and provides a view of the cavity. In the absence of a CSF leak, we do not repair the sellar floor so as to allow continued drainage.

38.3 Prognosis and Outcome

38.3.1 Prolactinomas

Prolactinomas are effectively treated with pharmacotherapy in as many as 89% of patients.^{12,48,49} If patients cannot tolerate the medications or if their tumors are refractory to the medications, surgical remission may be obtained in 85% of patients with microprolactinomas.

38.3.2 Corticotropinomas

The transsphenoidal resection of Cushing disease results in a surgical cure in the majority of children, with initial remission rates of 70 to 98% and long-term remission rates of 50 to 98%.^{31,32,50,51} Successful surgery results in remission of the signs and symptoms of hypercortisolism by normalization of laboratory values. Surgery is usually followed by adrenal insufficiency, and patients may require hydrocortisone replacement for 6 to 12 months. After normalization of the cortisol levels, resumption of normal growth or even catch-up growth can be observed. Generally, the patient's final height is compromised compared with his or her target height.³⁵ Some children, however, do achieve a normal final stature.

In the approximately 10% of patients with relapse or recurrence, the choice of treatment is controversial. Although repeated surgical resection can induce panhypopituitarism or permanent diabetes insipidus, hypothalamic–pituitary dysfunction is an early and frequent complication of radiation therapy.^{52,53} Conformal radiation therapy has a 2-year remission rate of approximately 70 to 80%.³⁵ Stereotactic radiosurgery with the gamma knife may further minimize the toxic effects of radiation on the brain, while still controlling tumor growth and ACTH secretion. Bilateral adrenalectomy may be the last therapeutic option in case of failure of both surgery and radiotherapy.

38.3.3 Somatotropinomas

Transsphenoidal resection for somatotropinomas is as effective in children as it is adults⁶ however, only approximately 60% of patients with acromegaly achieve normal GH levels.^{36,54} Patients with larger, more invasive tumors may benefit from adjuvant medical and radiation therapy to achieve long-term disease control.

Pearls

- Pediatric pituitary adenomas are rare entities that generally present with headaches, endocrine dysfunction, and/or visual disturbances.
- The evaluation of a pituitary mass includes contrast-enhanced MR imaging with dedicated pituitary imaging, a full evaluation of the hypothalamic–pituitary axis, and an ophthalmologic evaluation.
- Prolactinomas are the most common pediatric pituitary tumor, are usually diagnosed at the time of or following puberty, and are primarily treated with medical management.
- Corticotropinomas (Cushing disease) are primarily found in prepubescent children and are treated with transsphenoidal resection of the microadenoma.
- Somatotropinomas (acromegaly) are associated with gigantism and are primarily treated with surgery, although there may be a role for medical management.
- The early identification of pituitary adenomas and their management by a multidisciplinary team of endocrinologists and neurosurgeons are essential for disease control and normal growth and development of the child.
- Pituitary microadenomas are best removed in one piece with a pseudocapsular technique when possible.
- Pituitary macroadenomas may have to be removed in a sequential, piecemeal-type fashion, but every attempt should be made to resect the pseudocapsule.

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39 Pineal Region Tumors

Tadanori Tomita

39.1 Pineal Gland

The normal pineal gland measures only 5 to 10 mm. It is histologically composed of pinealocytes (95%) and glial cells (5%). Pinealocytes are a specialized form of neuronal cells and function as neuroendocrine transducers. In lower mammals, these cells exhibit structural characteristics of photoreceptor cells. In primitive animals such as fish and amphibians, the pineal gland is a neurosensory photoreceptor organ. In mammals, it has a neurotransmitter secretory function. The function of the pineal gland in humans is not well understood, however. The pineal gland is innervated by sympathetic nerve fibers that originate from the superior cervical ganglia. The pinealocytes play a role in translating the noradrenaline input released from sympathetic nerves into a hormonal input. The pineal secretory function, specifically melatonin and serotonin synthesis and release from the pinealocytes, has been studied extensively. Serotonin concentration in the pineal gland is highest in the brain. Melatonin release in animals follows a circadian rhythm, with high serum levels during the night and low levels during the daytime. Melatonin also has an inhibitory effect on the hypothalamic-pituitary axis and at the gonadal level.¹ However, in humans, although melatonin levels are highest between the ages of 1 and 5 years and then decrease until the end of puberty,² the function of melatonin remains unexplained.³

39.2 Pineal Region

The pineal region comprises multiple structures in and around the pineal gland of the posterior third ventricle. The pineal gland is bordered by the cerebrospinal fluid (CSF) space, the third ventricle anteriorly, and the quadrigeminal cistern posteriorly. The neural structures that surround the pineal gland are the quadrigeminal plate of the midbrain inferiorly, the cerebellar vermis posteriorly, and the splenium of the corpus callosum superiorly. Lateral to the pineal gland are the posterior thalami, and anteroinferiorly is the tegmentum of the midbrain, which is continuous anteriorly with the hypothalamus. The lateral wall of the third ventricle is traversed by a hypothalamic sulcus from the foramen of Monro to the aqueduct of Sylvius. This sulcus separates the thalamus above from the hypothalamus below. The roof of the third ventricle consists of the tela choroidea and fornix.

39.3 Pathology and Pathobiology

Heterogeneous types of tumors occur in the pineal region. Tumors of pineal and extrapineal origin differ in histologic type. Those of pineal origin are germ cell tumors and pineal parenchymal cell tumors. Extrapineal tumors arise from the surrounding neural or mesenchymal structures and include astrocytomas, meningiomas, ependymomas, and choroid plexus papillomas. Another tumor in this location with papillary features, papillary tumor of the pineal region, is considered to be derived from the subcommissural organ.^{4,5}

39.3.1 Germ Cell Tumors

Tumors of germ cell origin are classified as germinomas, embryonal carcinomas, endodermal sinus tumors (yolk sac carcinomas), choriocarcinomas, and teratomas. Germinomas, which are the most common of the germ cell tumors, are composed of cells with suppressed differentiation potential. On the other hand, embryonal carcinomas are considered to be composed of pluripotential cells. They further give rise either to embryonal tumors, which consist of all three germ layers (i.e., mature teratomas and immature teratomas) or to extraembryonal tumors. The latter include choriocarcinomas through trophoblastic differentiation and yolk sac tumors through yolk sac formation. Of all the germ cell tumors, only the mature teratoma is considered to be benign. Other, nongerminomatous tumors are malignant and are included in a category of nongerminomatous germ cell tumors (NGGCTs). Elements of various germ cell tumors may coexist in a single tumor; this type of tumor is called a mixed germ cell tumor. Teratomas, on the other hand, are derived from all three germ layers of embryonal structures and are composed of well-differentiated tissues with an organoid pattern. Those composed of mature cells are benign teratomas. Immature teratomas, however, contain primitive elements derived from all or any of the three germ layers and behave in a malignant fashion.

The origin of germ cell tumors is controversial. Germ cell tumors derive from pluripotential germ cells and span a wide range of differentiation and malignant characteristics.⁶ The primordial germ cells appear in the yolk sac wall in the third gestational week. They migrate from the fetal yolk sac via the dorsal mesentery of the hindgut into the genital ridge in the sixth gestational week. They also migrate and disseminate widely throughout various tissues and organs in the early embryo. In the extragonadal location, these germ cells often remain in two midline sites: the mediastinum and around the third ventricle. This theory explains why extragonadal germ cell tumors frequently develop in the thymus and in the pineal and hypothalamic regions. However, in normal human anatomy, the primordial germ cells are not found in these locations. Sano theorized that misplaced embryonic tissues incorrectly enfolded at the time of neural tube formation become the source of intracranial germ cell tumors.⁷ Despite their early migration, these germ cells tend to develop neoplastic transformation at a much later stage of life, around puberty. One assumes that gonadotropins or gonadotropin-releasing hormones secreted by the hypothalamus at puberty may have a carcinogenic effect.⁸

Intracranial germ cell tumors show genomic alterations indistinguishable from those of their extracranial counterparts; these include gain of 12p and the X chromosome.⁹ Also, mutation of the *c-KIT* gene is common among germinomas.¹⁰

39.3.2 Pineal Parenchymal Tumors

Pineal parenchymal tumors are derived from pineal parenchymal cells within the pineal gland. These tumors possess the potential to differentiate into several cell lines, such as neuronal,

astrocytic, ependymal, retinoblastomatous, and mesenchymal components. Pineal parenchymal tumors are classified into pineoblastoma, pineocytoma, and intermediate types, depending on the cellular differentiations.¹¹ Pineoblastomas are poorly differentiated malignant tumors and belong to the group of primitive neuroectodermal tumors (PNETs). Pineocytomas, on the other hand, are differentiated and clinically benign. Some parenchymal tumors may have mixed components of pineoblastoma and pineocytoma. On immunohistochemical studies, Yamane et al reported variable immunopositivity among pineal parenchymal tumors when they used monoclonal antibodies against human pineal tissue, whereas glial differentiation seemed very rare.¹² Ultrastructural studies found that neoplastic pineal cells appeared to differentiate either toward a neurosensory pathway characterized by the presence of sensory cell elements, such as vesicle-crowned rodlets and fibrous filaments, or toward a neuroendocrine pathway.^{13,14} Cytogenetic studies showed monosomy of chromosomes 20 and 22 and gain of 1q, 5p, 5q, 6p, and 14q.¹⁵ The gene patterns of the three pineal parenchymal tumors fell in the same cluster. The pineocytomas showed high expression of *TPH*, *HIOMT*, and genes related to phototransduction in the retina (*OPN4*, *RGS16*, and *CRB3*), whereas the pineoblastomas showed high expression of *UBEC2*, *SOX4*, *TERT*, *TEP1*, *PRAME*, *CD24*, *POU4F2*, and *HOXD13*.¹⁵ Papillary tumors of the pineal region showed high expression of *SPEDF*, *KRT18*, and genes encoding proteins reported to be found in the subcommissural organ, namely *ZFH4*, *RFX3*, *TTR*, and *CGRP*.¹⁵

39.3.3 Tumors of Glial and Miscellaneous Cell Origin

Astrocytes are normally present in the pineal gland, but pure pineal gland glial tumors are exceedingly rare. Nearly all glial tumors arise from the glial tissue elements intimately surrounding the pineal gland. Astrocytomas often originate in the thalamus or the midbrain and extend to the pineal region. Glioblastomas, astroblastomas, ependymomas, oligodendrogliomas, choroid plexus papillomas, and medulloepitheliomas may occur in this region. Among tumors of mesenchymal origin, meningiomas, hemangiomas, and cavernomas may occur in the pineal region.

39.3.4 Nonneoplastic Cysts

Pineal cysts, which result from focal degeneration of the pineal gland, contain gelatinous material. The cyst wall is composed of three layers: an outer fibrous layer, a middle layer of pineal parenchymal cells with variable calcification, and an inner layer of hypocellular glial tissue.^{16,17} Other developmental cysts include epidermoid and dermoid cysts. Arachnoid cysts consist of CSF and a cyst wall composed of arachnoid membrane. These cystic lesions may have a similar appearance on neuroimages.

39.4 Epidemiology

Pineal region tumors comprise 3 to 8% of all intracranial tumors among children.¹⁸ Pineal region tumors affect more Japanese and other persons of Asian origin.^{19,20}

Intracranial germ cell tumors account for 0.4 to 3.4% of intracranial neoplasms in the United States and Europe.⁸ Germinomas are the most common variety among them, comprising 35 to 41%^{1,21} or 61 to 65%^{8,22,23} of germ cell tumors. Their average incidence in the United States is considered to be 0.1 per 100,000 persons per year.²⁴ Germ cell tumors of the pineal region tend to affect males, with a male-to-female ratio of 4:1.^{8,21} Most germinomas occur in the first three decades, with a peak in the middle of the second decade, corresponding to the onset of puberty. About 65% occur between the ages of 10 and 21 years, and only 11% occur before the age of 9 years.

NGGCTs are highly malignant. Most cases of NGGCTs occur in males in the first two decades of life. Choriocarcinomas tend to occur at a younger age (mean age, 8 years) than do embryonal carcinomas and endodermal sinus tumors (mean age, 14 and 17 years, respectively). Of choriocarcinomas, 35% occur before the age of 9 years, whereas only 10 to 12% of embryonal carcinomas and endodermal sinus tumors occur before the age of 9 years.

Teratomas in the pineal region often affect males. Most teratomas occur in children younger than 9 years, but 20% occur in persons between the ages of 16 and 18 years.

The occurrence of mixed germ cell tumors has increased because of a recent trend of aggressive tumor biopsy and the availability of tumor marker studies. In a study by Matsutani et al, 49 (32%) of 153 intracranial germ cell tumors were of mixed type.²¹ The common components frequently present in mixed germ cell tumors are germinoma and teratoma, whereas a combination of germinoma and choriocarcinoma is very rare. The correct identification of mixed germ cell tumors and NGGCTs requires adequate tumor sampling and proper preparation of the tissue for immunohistochemical and electron microscopic examination.²³

Pineoblastomas often occur in infancy and childhood,²⁵ whereas pineocytomas occur in older children and young adults.^{11,14,26,27}

The ratio of germ cell tumors to pineal parenchymal tumors was reported to be 3.6:1, whereas germ cell tumors accounted for 31% of the tumors in 282 patients of all age groups with pineal region tumors.^{28,29} In Japan, germ cell tumors are much more common than pineoblastomas, which comprise only 5.1% of pineal region tumors.³⁰

39.5 Symptomatology

The common signs and symptoms of pineal region tumors are primarily related to increased intracranial pressure due to hydrocephalus, which is present in almost all cases. Hydrocephalus is the result of obstruction of the aqueduct of Sylvius. The most common symptom is headache. The headaches usually occur intermittently initially but become more frequent and intense. They are worse in the morning and often awaken the patient during sleep. Nausea and emesis are common signs in association with headaches. Double vision may be due to either abducens nerve palsy or tectal compression. Occasional blurred vision can be due to the tectal compression but can also be related to visual obscuration secondary to papilledema. In the later stages of hydrocephalus, patients exhibit an ataxic gait and altered mental status. Papilledema is a frequent sign of hydrocephalus secondary to pineal region tumors.

Other signs are related to direct compression of the neural tissue, particularly the quadrigeminal plate and pretectal region of the midbrain. Parinaud syndrome is well-known to be pathognomonic for pineal region tumors and is present in about 50 to 75% of patients with pineal region tumors. It is due to compression or structural damage on the posterior commissure. The sudden occurrence of the setting sun phenomenon and Parinaud syndrome together with decreased mental status may be related to hemorrhage into the pineal tumor (pineal apoplexy).

Synchronous germinomas in the pineal and suprasellar regions may present with diabetes insipidus and other hormonal dysfunctions and with visual impairment.³¹ Pineoblastomas and less often germinomas may have disseminated through the CSF pathway at the time of diagnosis, which may cause various signs such as spinal cord compression and optic nerve compression.³² Precocious puberty is rare^{21,33-35} and usually occur in boys with choriocarcinoma because β -human chorionic gonadotropin (β -HCG) secondarily stimulates androgen secretion by the Leydig cells of the testes.

39.6 Diagnostic Studies

39.6.1 Neuroimaging

Computed Tomography

Computed tomography (CT) and magnetic resonance (MR) imaging are helpful for tumor detection. Associated abnormalities, such as hemorrhage and calcifications, may be better appreciated with CT. Calcifications often occur in the pineal gland.

According to Zimmerman and Bilaniuk, the youngest subject with a normally calcified pineal gland was 6 1/2 years of age.³⁶ The rates of pineal calcifications detected on CT scans were 8 to 10% from the ages of 8 to 14 years, 30% at the age of 15 years, and 40% at the age of 17 years. The presence of calcifications in children younger than 6 years, however, is abnormal and needs to be investigated for a neoplastic process.³²

On CT scans, germinomas appear as soft tissue masses that are hyperdense relative to the surrounding brain tissue. Pineal calcifications of germinomas tend to be located centrally or displaced peripherally in the tumor mass, whereas calcifications of pineoblastomas, if present, are dispersed within the tumor (► Fig. 39.1). Teratomas tend to present as inhomogeneous hypodense multiple cystic lesions with variable contrast enhancement (► Fig. 39.2). After the infusion of intravenous contrast agent, germinomas tend to enhance homogeneously. NGGCTs tend to have similar homogeneous soft tissue density, and their calcification is also similar to that of germinomas. Choriocarcinomas may have hemorrhagic foci (► Fig. 39.3). On the other hand, the appearance of teratomas is more distinct and often heterogeneous, with a variable degree of soft tissues, calcifications, and cyst formation. Pineoblastomas are relatively homogeneous and hyperdense on precontrast CT scans. After the infusion of contrast material, enhancement ranges from dense to little or none. Calcifications can occur either centrally or peripherally, but calcification is rare in pineoblastomas. There are no characteristic CT features to differentiate among pineal germ cell tumors other than teratomas and pineal parenchymal tumors.

Benign astrocytomas are often hypodense relative to the surrounding brain tissues on precontrast CT scans. They primarily

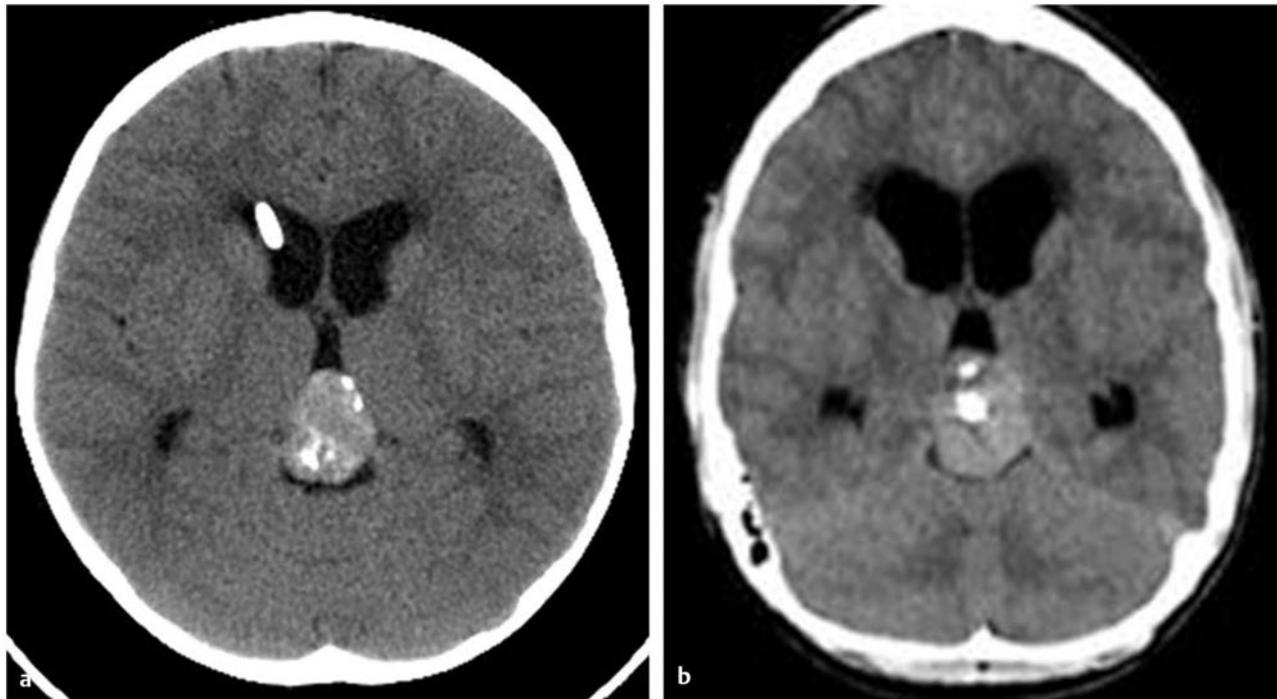


Fig. 39.1 Pineal calcification on precontrast computed tomographic scans. (a) Calcifications may be located centrally or peripherally in germinoma. (b) Calcifications may be dispersed in pineoblastoma.

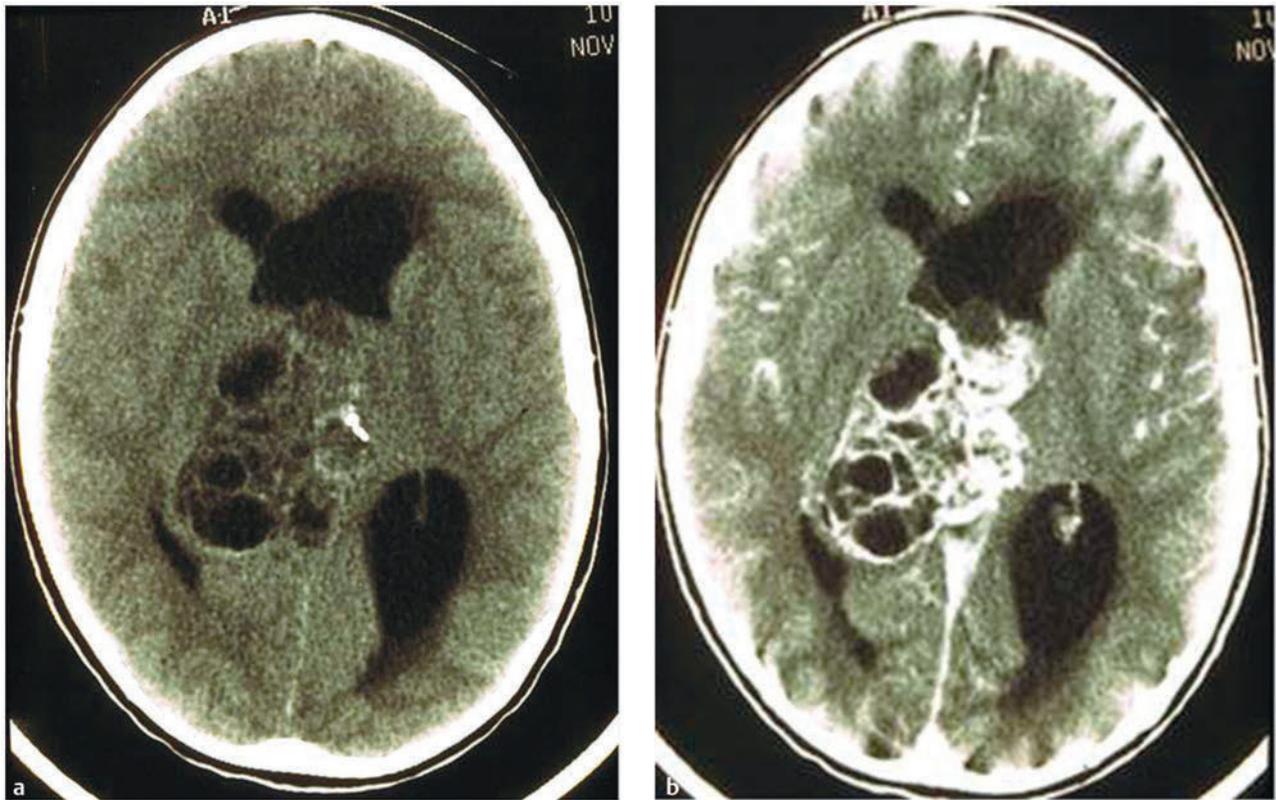


Fig. 39.2 Pineal calcification on precontrast computed tomographic scans. (a) Calcifications may be located centrally or peripherally in germinoma. (b) Calcifications may be dispersed in pineoblastoma.

originate from the midbrain or the posterior thalamus. They may be cystic, but calcification is uncommon. Contrast enhancement is variable and often inhomogeneous. Dermoid and epidermoid tumors tend to be hypodense and enhance minimally after the infusion of contrast material. They may have density equal to that of CSF, and their appearance may mimic that of an arachnoid cyst or pineal cyst.

Magnetic Resonance Imaging

Teratomas are often heterogeneous, with the presence of cyst formation and fat (► Fig. 39.4). Germinomas show low signal intensity to isointensity on T1-weighted images. They show high signal intensity or are isointense on T2-weighted images.³⁷ After the infusion of contrast material, germinomas show enhancement. Malignant NGGCTs may show variable signal intensity that is partly due to the presence of hemorrhage.³⁸ Pineoblastomas are hypo- or isointense on T1-weighted images, and variable degrees of enhancement are noted with poorly defined margins.³⁹ In general, the MR imaging signal characteristics are usually nonspecific,^{36,38} and correlation with the patient's age, sex, and other associated factors needs to be analyzed for diagnostic purposes.³⁹ Concurrent masses in both the anterior and posterior parts of the third ventricle strongly suggest germ cell tumor, germinoma in particular (► Fig. 39.5). Rates of occurrence of multiple germinoma lesions in the third ventricle may vary: 6.0 to 8.5%,^{8,21} 15%,⁴⁰ or 32 to 57% of cases.^{37,40,41} The frequency of

this multiplicity has increased with the use of more sensitive neurodiagnostic methods. For instance, Sugiyama et al reported that the frequency of synchronous lesions in pineal and suprasellar germinomas increased from 4.2% before to 17.4% after the introduction of MR imaging.³¹ In my personal experience with 43 patients who had pineal germ cell tumors treated from 1988 to 2010, 12 (28%) showed synchronous anterior and posterior third ventricle lesions. Of these 12 patients, 10 presented with diabetes insipidus. When a patient with a pineal region tumor presents with diabetes insipidus, the pituitary stalk and the tuber cinereum should be carefully investigated in order to detect multiplicity of the lesions.

Among patients with either unilateral or bilateral retinoblastomas, 3% have pineal parenchymal tumors (trilateral retinoblastoma). A history of retinal disease or evaluation with neuroimaging of the orbits enables the differentiation of pineoblastomas from other tumors in such a case.

Pineal region tumors are frequently associated with hydrocephalus. Pineal cysts, which are present in 2.4% of the normal population, are rarely symptomatic and usually remain stable in size.¹⁶ They have a contrast-enhancing cyst wall and subtle hyperintensity of the cyst contents. Mostly, they are single cysts, although occasionally a multicystic appearance is noted. Large cysts occasionally show radiographic evidence of tectal compression despite the absence of hydrocephalus. The occurrence of hydrocephalus is very rare. Fain et al reported that of 20 patients with symptomatic pineal cyst, 8 were noted to be hydrocephalic.¹⁷

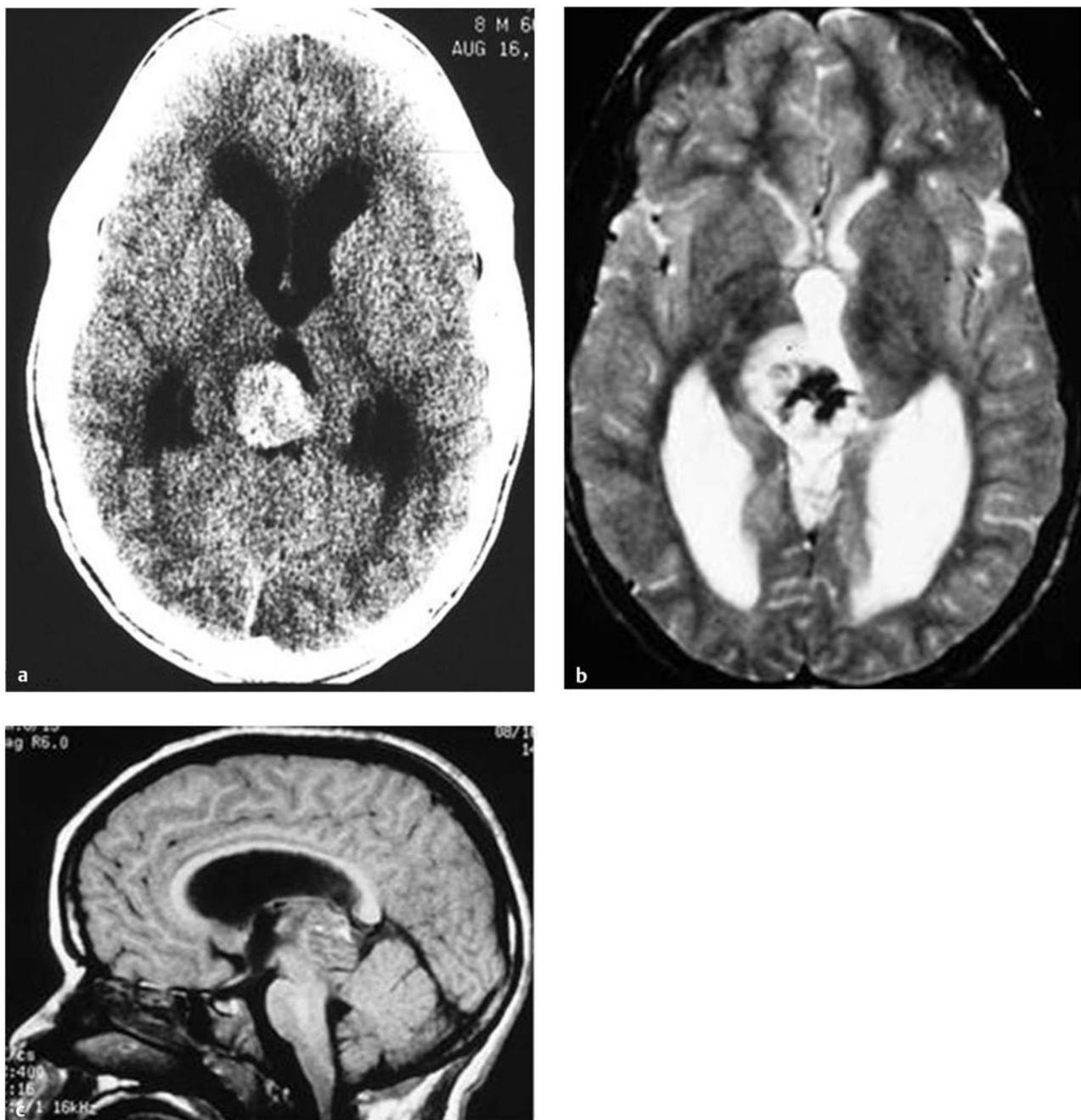


Fig. 39.3 (a) Hemorrhagic choriocarcinoma is shown on precontrast computed tomographic scan, (b) T2-weighted axial magnetic resonance (MR) image, and (c) T1-weighted sagittal MR image.

A nonenhancing thick quadrigeminal plate that causes obstructive hydrocephalus rarely requires surgical biopsy. No histologic data are available for these lesions because of the lack of pathologic verification. Contrast enhancement within the lesion may vary during follow-up despite a stable size over years. Some may show an exophytic nature, projecting beyond the quadrigeminal plate, and/or contrast enhancement, mimicking a pineal tumor.

Once a pineal region tumor is diagnosed, MR imaging of the spine needs to be obtained for staging purposes. Some malignant tumors, pineoblastomas in particular, may present with diffuse dissemination in the subarachnoid space.

39.6.2 Laboratory Tests

Certain germ cell tumors manifest tumor markers that are identified in the serum and CSF. Identification is important not only for diagnostic purposes but also for monitoring responses to treatment and relapses.³⁶ Alpha fetoprotein (AFP), a glycoprotein, is normally produced by the yolk sac and the fetal liver, but its production ceases by the time of birth. An AFP value of less than 5 ng/mL in the serum and CSF is considered to be normal.⁴⁰ In the central nervous system, yolk sac tumors (endodermal sinus tumors) show the greatest production of AFP.

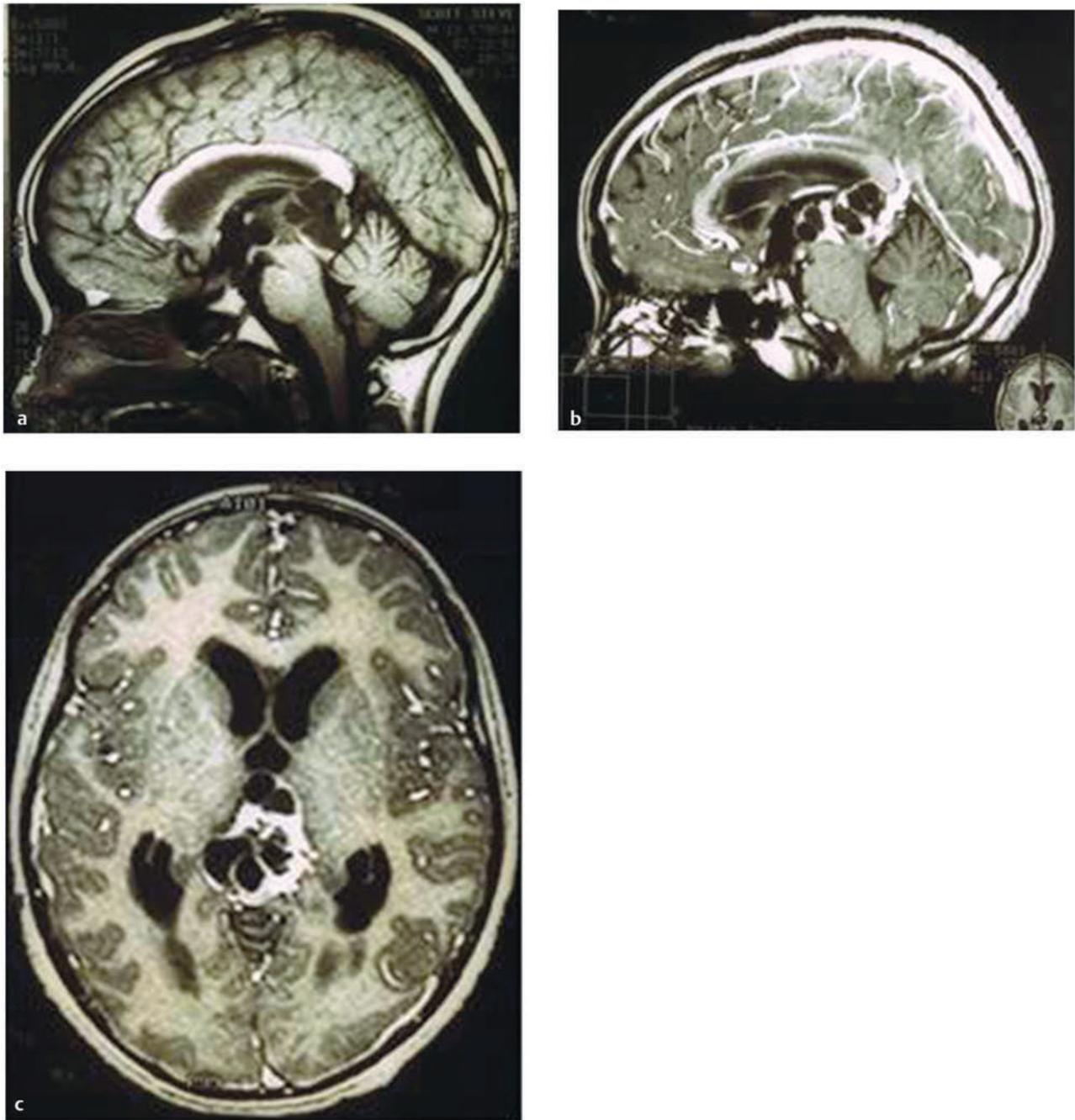


Fig. 39.4 (a) Mature teratoma is shown on precontrast sagittal magnetic resonance (MR) image. (b) Note inhomogeneous enhancement on postcontrast sagittal and (c) axial MR images.

Embryonal carcinomas and immature teratomas produce AFP to a lesser extent ($< 1,000$ ng/mL). β -HCG is a glycoprotein that is normally secreted by syncytiotrophoblastic giant cells in placental trophoblastic tissue. Therefore, the presence of β -HCG strongly indicates germ cell tumors. The normal value in the serum and CSF is less than 5 mIU/mL.⁴⁰ Marked elevation of β -HCG above 2,000 mIU/mL is noted in choriocarcinomas, but mild elevations (< 770 mIU/mL) can occur in patients with germinomas and embryonal carcinomas. The biological half-life is

about 5 days for AFP, whereas it is less than 24 hours for β -HCG. The titers of β -HCG and AFP reflect the number of cells secreting these glycoproteins; this information is useful for differentiating tumors that are predominantly choriocarcinoma or yolk sac tumor, but not confirmative for histologic diagnosis.²¹ Abnormal AFP and/or β -HCG levels in the serum or CSF are generally regarded to indicate NGGCTs.⁴²

Malignant germ cell tumors show positivity for tumor markers, either β -HCG or AFP or both, in 39 to 70% of cases.^{21,37}

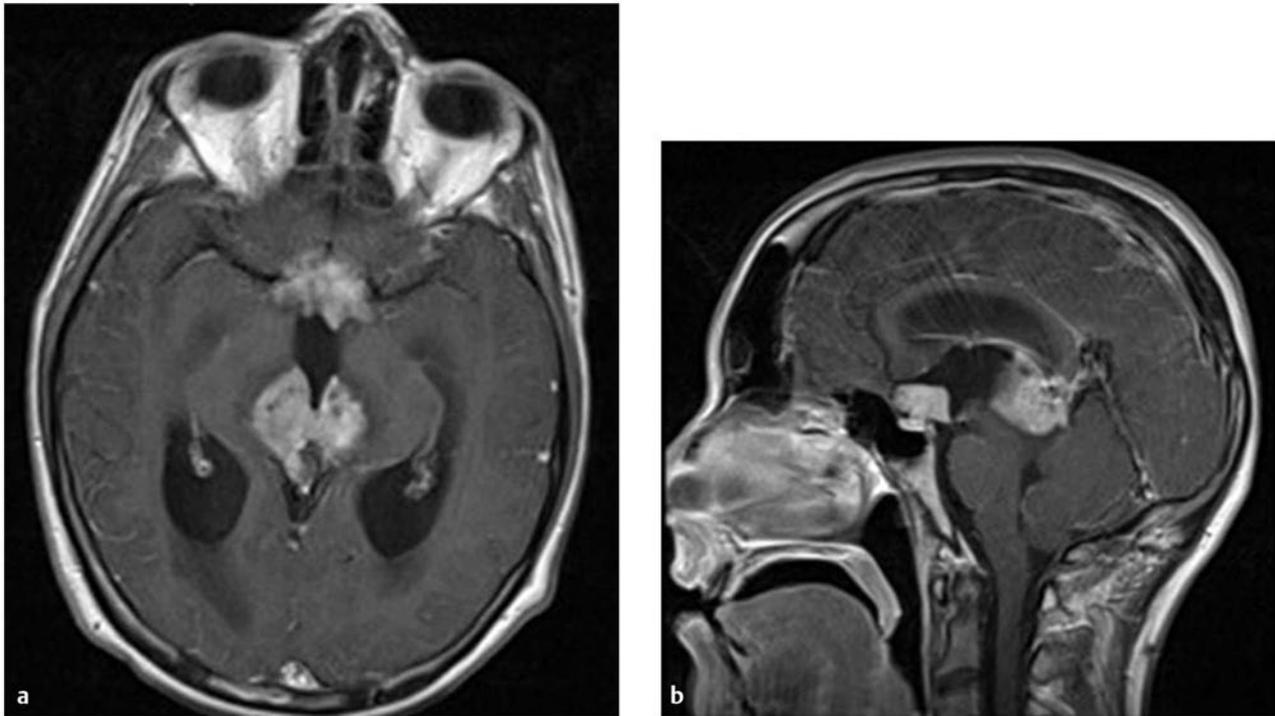


Fig. 39.5 (a) Axial and (b) sagittal magnetic resonance images after contrast infusion showing concurrent germ cell tumors with elevated serum alpha fetoprotein in the pineal and suprasellar locations.

The results of positivity for these tumor markers are variable; some report more frequent positivity for AFP⁴³ and others vice versa.⁴⁴ However, our observations (T. Tomita, unpublished data) and those of others⁴⁵ indicate that the β -HCG value tends be higher in the CSF than in the serum.⁴⁵ Thus, it is important to obtain the values of tumor markers from both serum and CSF.

Placental alkaline phosphatase (PLAP) was reported as a specific marker for primary intracranial germinomas.⁴⁶ PLAP is distinguished from other common tissue alkaline phosphatases by its heat resistance and its inhibition by L-phenylalanine. PLAP levels in serum or CSF are measured with an enzyme-linked immunosorbent assay, but their sensitivity and specificity need further investigation. The CSF in five of nine patients with germinoma showed high levels of PLAP.⁴⁷ However, reliable methods to measure PLAP in the CSF have not been available. The proto-oncogene *c-KIT*, which encodes tyrosine kinase for the stem cell factor, is expressed on the cell surface of germinoma. The concentration of the soluble form of the *c-KIT* receptor (*s-KIT*) is significantly high in the CSF among patients with germinoma.^{10,48} The melatonin level may be used as a tumor marker for pineal tumors. Melatonin secretion by the pineal gland follows a nyctohemeral rhythm. When the pineal gland is disturbed by invasive tumors such as germinoma or NGGCT, the melatonin rhythm is dramatically reduced. However, the diagnostic value of melatonin profiles is limited in clinical practice.⁴⁹ Low serum levels of melatonin may be used as a marker for pineal tumors that destroy the pineal gland.⁵⁰ High nighttime melatonin levels have been reported among patients with pineocytomas, whereas depressed melatonin secretion has been observed among patients with pineal cysts.⁵¹

39.6.3 Cerebrospinal Fluid Cytology

The CSF, whenever available, either by means of lumbar puncture or from the ventricle at shunt placement, third ventriculostomy, or external ventricular drainage, should be analyzed with cytologic studies together with tumor markers for pineal region tumors. The frequency of CSF dissemination among malignant germ cell tumors varies from 3%^{43,44} to 36 to 52%.⁵² On the other hand, pineoblastomas disseminate along the CSF pathway with higher frequencies of 50% at diagnosis and almost 100% at terminal stage.^{16,53}

39.6.4 Biopsy

Histologic verification on the basis of tumor markers and/or biopsy leads to an appropriate selection of therapeutic mode. There are several modes of biopsy: stereotactic biopsy, neuroendoscopic biopsy, and open biopsy.

Stereotactic Biopsy

Most reports indicate that the risks of surgical intervention are minimal.^{54,55} However, it is a serious potential concern that stereotactic procedures may result in hemorrhagic complications because tumors originating from the pineal gland are surrounded by deep veins of the lesser galenic system. Also, some tumors, such as pineoblastomas and choriocarcinomas, are often extremely vascular. In my experience with 14 stereotactic biopsies of pineal region tumors, two patients (one with germinoma and one with pineoblastoma) experienced a serious hemorrhage into the tumor and ventricle. However, other authors

have reported no major complications due to the stereotactic procedure.⁵⁵

Neuroendoscopic Biopsy

Neuroendoscopic tumor biopsy from the third ventricle became popular after recent advances in endoscopic instrumentation. The use of an image-guided neuronavigational system aids in localization of the tumor at endoscopic biopsy. Endoscopic biopsy can be performed at the same time as endoscopic third ventriculostomy (ETV).⁵⁶⁻⁵⁸ The pineal region tumor, however, is often difficult to visualize in the posterior third ventricle when a standard trajectory is used for the third ventriculostomy. In order to overcome this difficulty, one may use a flexible scope or a 30-degree-angle rigid scope,⁵⁷ or create another bur hole that is placed farther anteriorly.⁵⁶ Occasionally, unexpected tumor seeding may be recognized though endoscopic observation that may not be apparent on neuroimaging evaluation. Hemostasis can be achieved with a bipolar cautery. However, controlling a major hemorrhage is very difficult because of the limited field for ventriculoscopic instrumentation compounded by poor visibility due to hemorrhagic CSF. Wong et al postulated that intratumoral hemorrhage during and after endoscopic procedures for pineal tumors may be due to loose tumor tissue, hypervascularity in the tumor, and abrupt reduction in the intracranial pressure to zero during endoscopic procedures.⁵⁹ If significant hemorrhage occurs, the ventricular space should be irrigated until the returning fluid become clear. The patient may need temporary external ventricular drainage.

The tumor samples obtained with either a stereotactic procedure or ventriculoscopy are small. The pathologic diagnosis, however, can in most cases be determined from these small tumor samples. In cases of mixed malignant tumors, however,

heterogeneous components may be overlooked, and a small sample obtained with these methods may not indicate the true nature of the tumors.

39.7 Treatment

39.7.1 Hydrocephalus

Hydrocephalus may be controlled with either tumor mass reduction or a CSF diversion procedure. The surgical or nonsurgical reduction of a tumor in the pineal region would open the occluded aqueduct of Sylvius. Certain germ cell tumors can be considerably reduced in size in a short time following radiation therapy (RT) or chemotherapy, and hydrocephalus is resolved without surgery. However, these nonsurgical methods of tumor mass reduction require at least several weeks. Steroid therapy may be used for hydrocephalus pending the efficacy of RT or chemotherapy. Germinomas that contain a significant number of T-lymphocytes may be reduced in volume following steroid therapy (► Fig. 39.6).

A ventriculoperitoneal shunt was often used in the past. Placement of the shunt promptly improves the patient's condition. Concerns of the shunt, however, are potential risks for peritoneal metastases through the shunt and shunt dependency.

Recent advances in neuroendoscopic technology have enabled us to perform ETV. Successful hydrocephalus control is reported in 80% of patients with pineal region tumors.⁵⁸ The posterior third ventricle can be inspected and tumor biopsy can be performed at the same time as ETV. I routinely place an Omaya reservoir connected to the ventriculostomy catheter during the ETV that is helpful for subsequent ventricular access.

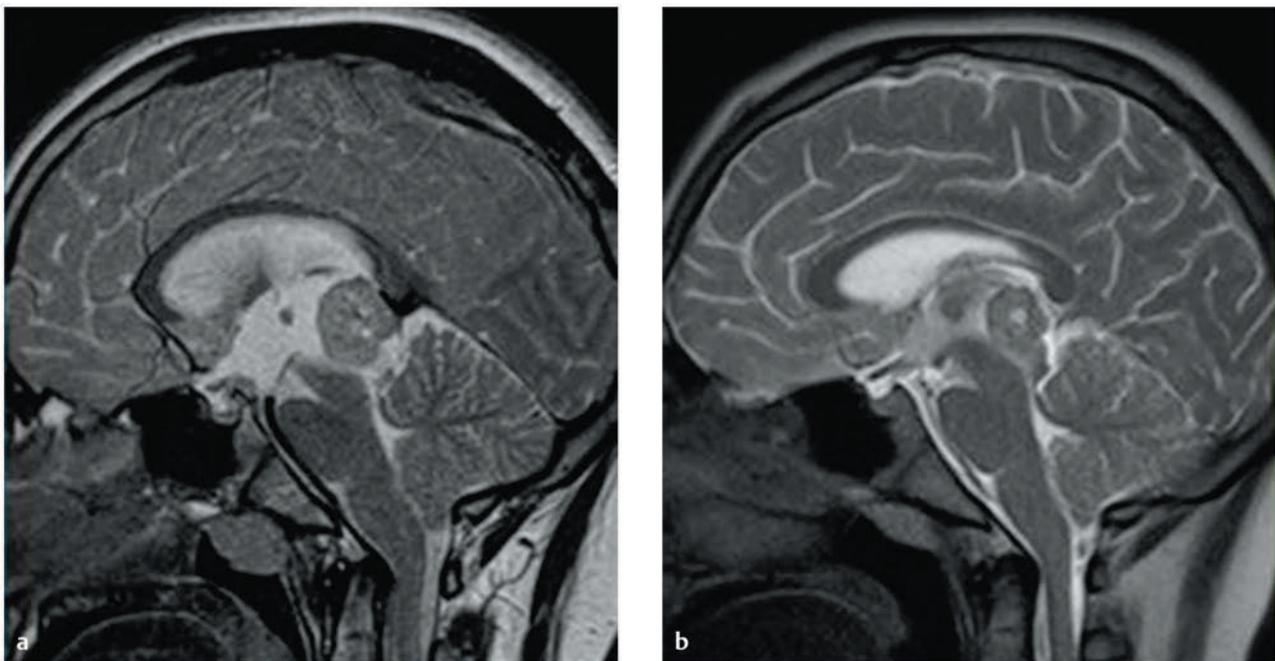


Fig. 39.6 (a) T2-weighted sagittal magnetic resonance image showing hydrocephalus secondary to pineal germinoma. (b) Following 3 days of treatment with dexamethasone, the tumor and hydrocephalus decreased in size.

39.7.2 Craniotomy

In 1921, Dandy initially described a parietal interhemispheric transcallosal approach.⁶⁰ Later, Horrax in 1937⁶¹ and subsequently Poppen in 1966⁶² developed an occipital transtentorial approach through a supratentorial craniotomy. The infratentorial route is primarily approached along the superior surface of the cerebellum and the inferior surface of the tentorium. This infratentorial supracerebellar approach was first described by Krause in 1926⁶³ and was popularized by Stein.⁶⁴

The current success in pineal tumor resections has been made possible by the surgical microscope, microsurgical instrumentation, established surgical approaches, and advanced neuroimaging studies. Intraoperative imaging guidance is also helpful. Approaches are either supratentorial or infratentorial.⁶⁵ The supratentorial routes include an occipital transtentorial approach, posterior interhemispheric approach, posterior interhemispheric transcallosal approach, anterior interhemispheric transcallosal approach, and lateral transventricular approach.

Each approach has advantages and disadvantages, and the approach should be chosen on the basis of the anatomical information provided by neurodiagnostic images, along with the surgeon's familiarity with and confidence in using the approach. The tumor location and extent, the deep venous system, and the surrounding neural structures need to be considered when the surgical approach is chosen. Other factors are the patient's age, presence or absence of hydrocephalus, shape of the head, and purpose of the surgery (biopsy vs. total resection). I personally prefer the supratentorial approach because pineal region tumors in children tend to be large and extend in various directions, and also because the posterior fossa space in infants and children is relatively small. The supratentorial approach provides a wide range of trajectory angles through a large interhemispheric avenue.

Supratentorial Approach

Occipital Transtentorial Approach

The prone position is used routinely, although some prefer a sitting position. I personally prefer to place all pediatric patients in a prone position with the head turned slightly (about 15 degrees) away from the surgical side if the patient is old enough to receive head pins for a head holder. This position is designed to let gravity cause the occipital lobe fall away from the falx, without the need for forcible brain retraction. Some choose a recumbent position for that reason.⁶⁶ If the patient is very young, when a pin fixation device is not applicable, the head is rested on a well-padded horseshoe head holder; the head is not turned. Brain retraction is controlled by means of intraoperative ventricular drainage for the interhemispheric approach. Retraction of the occipital and parietal lobes is more restricted when the ventricle is small or slitlike. One should avoid forcible retraction of the occipital lobe. The brain needs to be relaxed with the administration of mannitol, or sometimes by externalizing an existing shunt intraoperatively.

The occipital transtentorial approach provides a wide surgical entry for access to the pineal region. One can select from a wide range of angles of entry through a craniotomy that extends from the inion to the entry site of the last cortical vein into the superior sagittal sinus, which is usually 3 to 5 cm rostral to the

lambda. Exposure of the lateral sinus is not necessary because the approach is not suboccipital (lifting the occipital lobe) but through the interhemispheric fissure along the falx. Through a hockey stick skin incision (► Fig. 39.7), a craniotomy is usually placed that is approximately 10 cm in length and 5 cm in width and crosses over the superior sagittal sinus to the opposite side (► Fig. 39.8). At the entry of the interhemispheric fissure, there usually are no cortical veins posterior to the posterior parietal region. In my experience with 68 posterior interhemispheric approaches, only one patient had a significant draining vein from the occipital pole. However, Davidson et al stated that 7 of 27 patients needed bridging vein sacrifice through this approach.⁶⁶

Once the posterior interhemispheric fissure is entered along the falx, the splenium of the corpus callosum, the straight sinus, and the ipsilateral tentorium are in the surgical view (► Fig. 39.9a). The ipsilateral tentorium is sectioned approximately 1 cm lateral to the straight sinus in a length of 2 to 3 cm, exposing the underlying superior vermis (► Fig. 39.9b). This approach provides the surgeon with adequate exposure that ranges from the upper posterior fossa caudally and the anterior portion of the third ventricle rostrally. The vein of Galen is overlying the tumor when approached from the occipital and posterior parietal regions (► Fig. 39.9c). The microscope trajectory needs to be adjusted to a more horizontal angle to separate the dorsal surface of the tumor from the vein of Galen and its tributaries and to further visualize deep into the third ventricle. The only difficult area to expose is the opposite side beyond the falx. The contralateral portion of the tumor is brought into the surgical view by gradually retracting the tumor capsule following

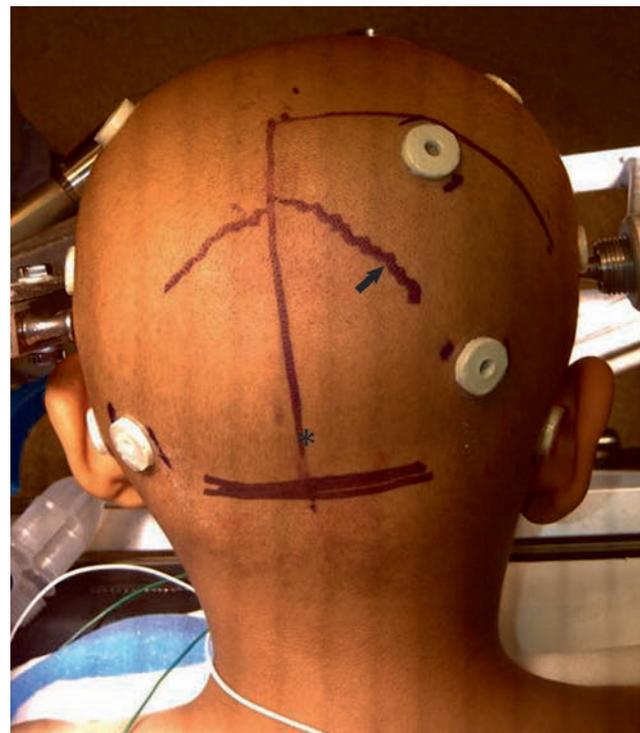


Fig. 39.7 Hockey stick skin incision for a right-sided occipital craniotomy and an occipital transtentorial approach. Note the right-sided lambdoid suture (arrow) and the inion (asterisk).

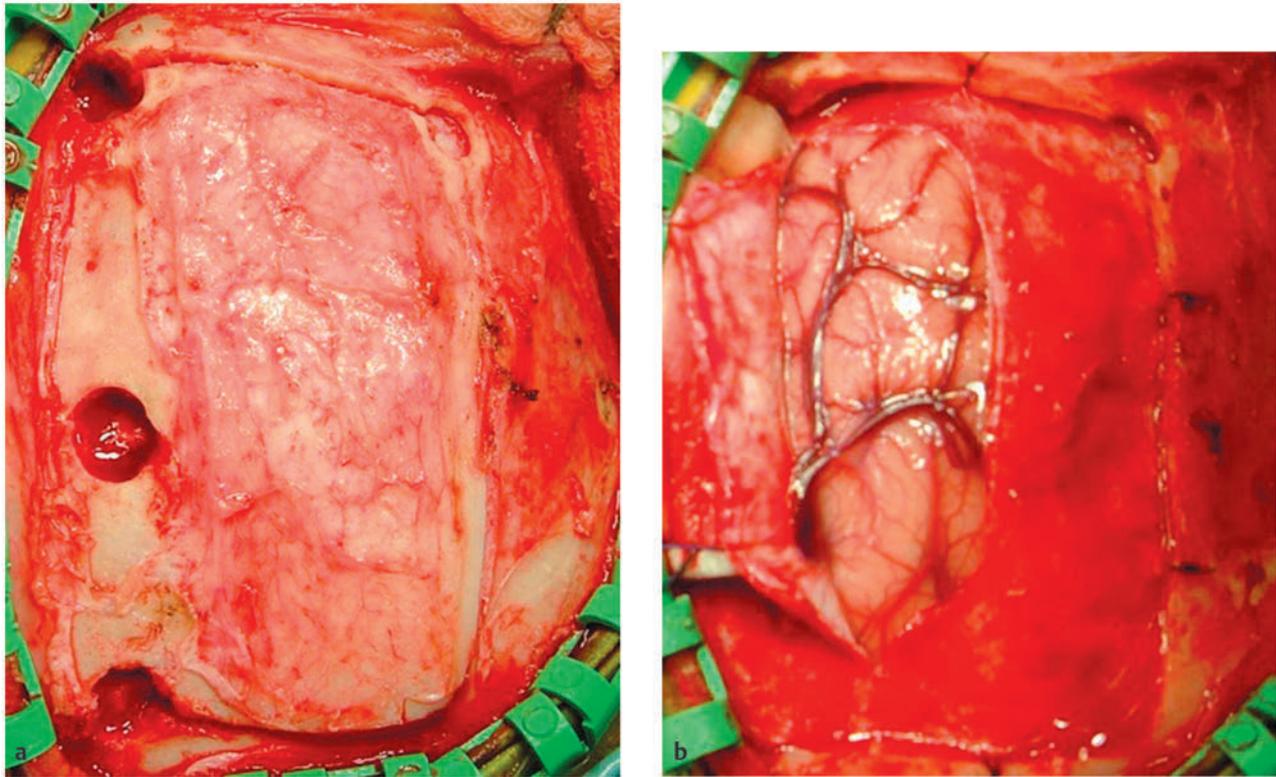


Fig. 39.8 A left occipital craniotomy for the occipital transtentorial approach is shown. (a) Bur holes are placed, one at 3 cm above, another just at the lambda, and the third one above the inion in the midsagittal plane. (b) A craniotomy extending beyond the midline is lifted.

internal decompression and reduction of the tumor bulk. The intraoperative use of a neuroendoscope is helpful to inspect this area and enhance the resectability.⁶⁷

When the microscope trajectory is adjusted vertically, the posterior surface of the tumor and the superior vermis are visualized through the sectioned tentorium. A large exposure in the upper posterior fossa, the quadrigeminal plate, the superior medullary velum, and the superior vermis is attained. A pineal region tumor that extends through the superior medullary velum to the fourth ventricle can be removed with this approach. For resection of a tumor in the anterior portion of the third ventricle, one can adjust the surgical microscope trajectory to angle horizontally. Following a successful tumor resection, the structures of the anterior wall of the third ventricle are within the surgical view (► Fig. 39.10). Sectioning of the splenium of the corpus callosum is rarely necessary. However, it may be necessary for resection of a massive tumor of the third ventricle, or if the space between the quadrigeminal plate and the vein of Galen is too tight to allow entry into the third ventricle. If the tumor originates from the posterior thalamus or is growing into the atrium of the lateral ventricle, the retrosplenial parahippocampal gyrus is retracted farther laterally.

Anterior Transcallosal Approach

Although some contend that sacrificing the middle third of the superior sagittal sinus cortical bridging veins does not cause permanent deficits,⁶⁸ others recommend using an anterior interhemispheric transcallosal approach, minimizing the risks for

venous infarct of the motor centers.⁶⁹ The patient is placed in a supine position with the head in the neutral position. The craniotomy is placed 4 to 5 cm anterior and 1 to 2 cm posterior to the coronal suture, crossing the midline. The ipsilateral anterior interhemispheric fissure is entered after one or two bridging veins are coagulated and sectioned, which usually is not of clinical significance. The corpus callosum is sectioned about 2 cm at its anterior body, which allows exposure of the ipsilateral lateral ventricle.

When the third ventricle is totally occupied by a large tumor that extends farther into the lateral ventricle, either through the foramen of Monro or beneath the tela choroidea, an anterior interhemispheric transcallosal approach is preferable through a posterior frontal craniotomy. This approach allows the surgeon to resect the tumor through the subchoroidal route. Because the tumor mass is already lifting the roof of the third ventricle, the subchoroidal space is stretched and widened in the medial wall of the lateral ventricle, and one can readily reach the entire third ventricular space through the subchoroidal space.

A transcallosal interforniceal approach through an anterior interhemispheric approach has been advocated recently for pineal region tumors.⁶⁹ Through a unilateral frontal craniotomy and interhemispheric approach, the anterior corpus callosum is sectioned about 2 cm. The interforniceal space is separated just above the foramen of Monro and then posteriorly. It is important to stay strictly on the midline by identifying the attachment of the septum pellucidum to the fornices. If one can enter the cavum septi pellucidi, the separation of the interforniceal space is less laborious. Through the space between the internal

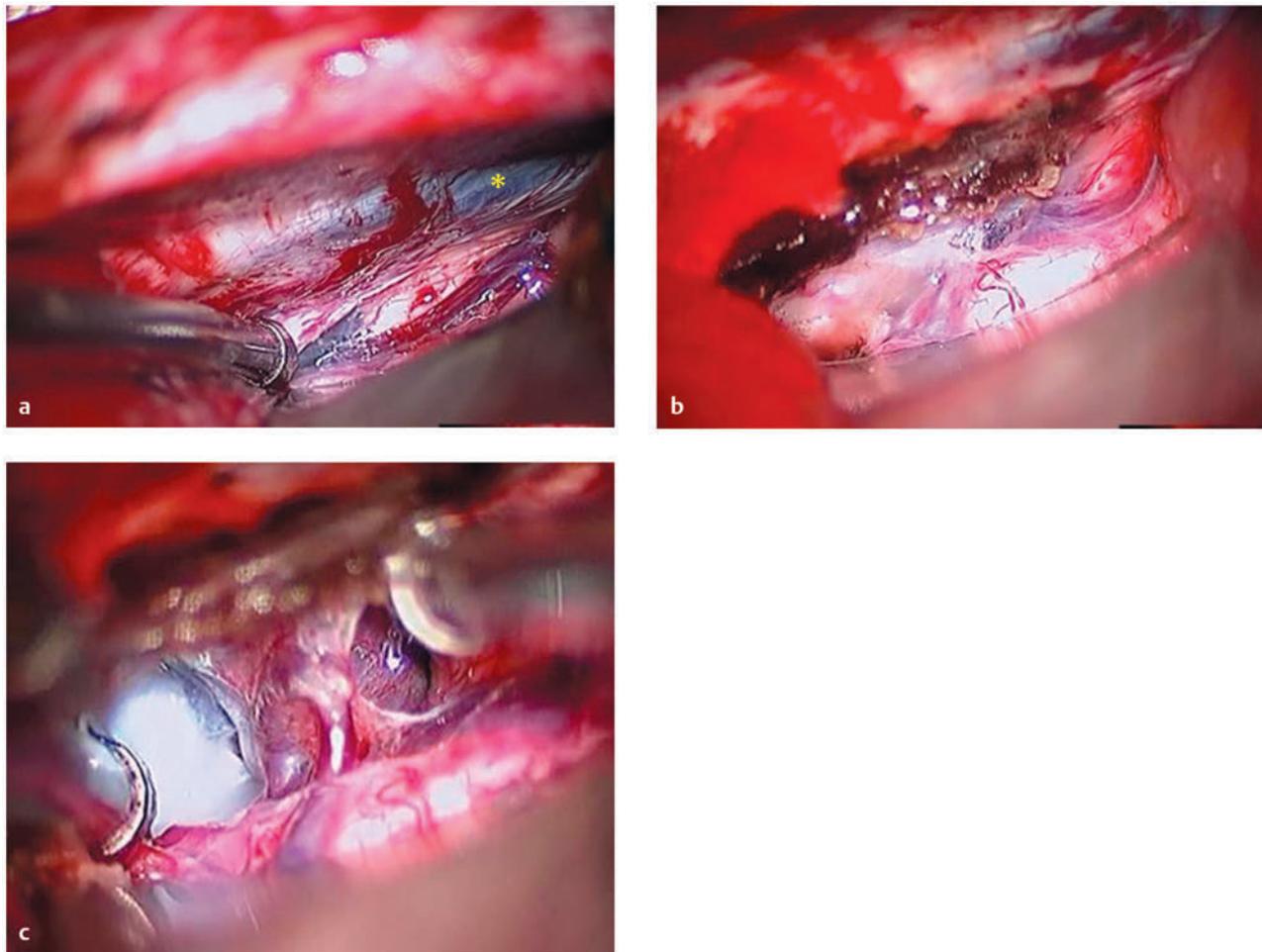


Fig. 39.9 An intraoperative photograph showing the posterior interhemispheric approach. (a) Note the posterior falx, the straight sinus (*asterisk*), and the tentorium, with partial exposure of the splenium of the corpus callosum. (b) The tentorium is sectioned, and the pineal region is in surgical view. (c) Following the opening of the arachnoid membrane of the quadrigeminal cistern, the vein of Galen and the tumor capsule are visible.

cerebral veins in the tela choroidea, the third ventricle is entered. It is necessary to section the massa intermedia to visualize the posterior third ventricle mass. Jia et al reported a high success rate of gross total resection of pineal region tumors in children when they used this approach. However, they had a high incidence of postoperative short-term memory deficit in 94 of 150 patients, although the memory deficits were usually transient and resolved within 6 months.⁶⁹

Infratentorial Approach

Infratentorial Supracerebellar Approach

Through a midline posterior fossa craniotomy, both lateral sinuses should be in the surgical field. The several superior vermian veins need to be sectioned along with the precentral vein to access the pineal location. The superior vermis is depressed, and the microscope trajectory is adjusted to avoid injuring the vein of Galen. The advantage of this approach is the midline trajectory, approaching the center of the tumor between the cerebellum and tentorial opening. The deep venous system is above and to the side of the tumor; thus, it is not disturbed during tumor resection. If a sitting position is used, gravity works in the

surgeon's favor because the tumor falls away from the galenic system above, minimal force is required for cerebellar retraction, and the surgical field is dry because blood and CSF are drained out by gravity. If the tumor is above the galenic system, however, it is difficult to remove it through this approach.

A concern with the use of the sitting position is the development of air embolism and hypotension. Young children, who cannot tolerate head pins for fixation, are difficult to place in the sitting position. When a sitting position is used, associated hydrocephalus needs to be decompressed before craniotomy. Otherwise, gravity will force the CSF out from the open third ventricle, which can result in acute collapse of the ventricular system and subdural hematoma or pneumocephalus. For the infratentorial supracerebellar approach, some surgeons prefer the Concorde (modified prone) position to avoid the sitting position.⁷⁰

In infants and young children, the posterior fossa is small and the distance from the foramen magnum to the torcular Herophili may be only 3.5 to 4.0 cm. Some older children or adults, particularly those with a flat occiput, may have a low-setting torcular Herophili. In these anatomical conditions, the surgical field through a supracerebellar approach is often restricted.

Depressing the cerebellum to expand the surgical opening and sectioning the vermian veins can result in postoperative cerebellar swelling. Particularly the portion of the tumor in the region of the superior medullary velum requires further depression of the superior vermis. It is difficult to remove tumors

located above the deep venous system or laterally beyond the tentorial opening, or extending into the lateral ventricle. More recent authors advocate an endoscopically controlled resection of pineal lesions through an infratentorial supracerebellar approach.⁷¹

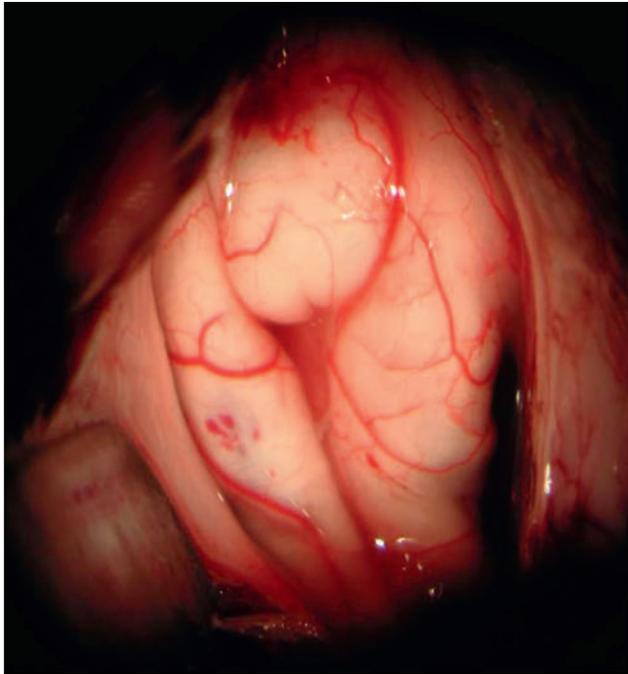


Fig. 39.10 Intraoperative photograph showing the anterior third ventricle following the tumor resection. Note the column of the fornix on each side, with the anterior commissure (*asterisk*).

39.7.3 Tumor Resection

The quadrigeminal cistern has a thick arachnoid membrane. Once the arachnoid membrane is opened, pineal tumors are exposed in the quadrigeminal cistern under the vein of Galen. Glial tumors may be covered by a thin cortex of either the quadrigeminal plate or the posterior thalamus. In such a case, one may identify a grayish pineal gland in the vicinity of the tumor. Pineal germinomas are well encapsulated, granular, and fibrous. Teratomas have a distinct capsule that often contains multiple cysts with light to thick mucoid contents. The inner structures of most teratomas are firm, and some are too fibrous and rubbery to aspirate by means of an ultrasonic aspirator. A tedious piecemeal resection is needed. In such a case, a surgical laser is quite helpful. Choriocarcinomas and yolk sac tumors are vascular, yet encapsulated. Old blood clot may be present within the tumor. Some tumors are extremely vascular, and one may need to terminate further surgical resection. Pineoblastomas are mostly soft and necrotic. They can often be suctioned away, but they are frequently very vascular because of tumor neovascularization.

Astrocytomas of the quadrigeminal plate or of thalamic origin are also resectable. On opening the quadrigeminal cistern, one should stay in the midline above the superior colliculi or identify the exophytic portion to debulk the mass. One should avoid traumatizing the inferior colliculi to prevent postoperative hearing loss. Thalamic astrocytomas may be approached

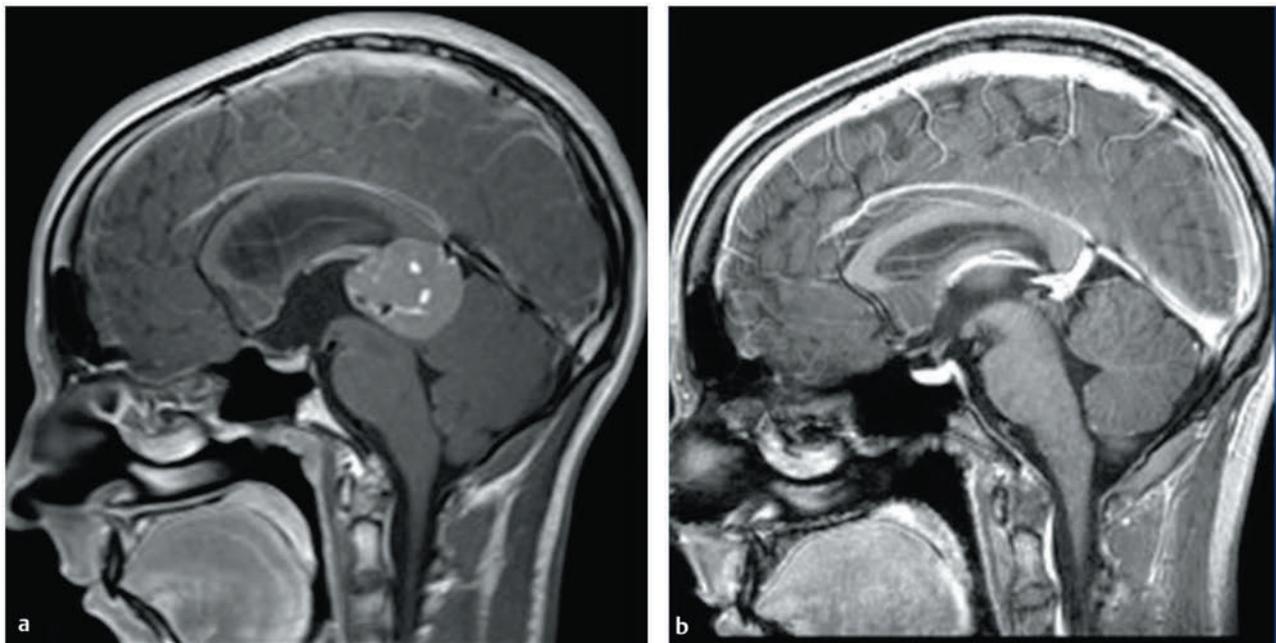


Fig. 39.11 Postcontrast sagittal magnetic resonance image of biopsy-proven germinoma (a) before and (b) 3 months after two cycles of chemotherapy. Note the rapid response of the tumor to the chemotherapy.

through the quadrigeminal cistern when the pulvinar is primarily involved. Benign astrocytomas are often well demarcated, and a gross resection is possible if one chooses the appropriate surgical approach.

39.7.4 Surgical Complications

In recent studies, surgical mortality is nearly zero. With an occipital transtentorial approach, retraction of the occipital lobe can cause hemianopia, although this is almost always transient.⁷² Retraction of the cerebellum together with sectioning of the superior vermian veins may result in postoperative cerebellar swelling following the infratentorial supracerebellar approach. Manipulation of the quadrigeminal plate and the posterior commissure may result in persistent or worsened Parinaud syndrome. This is due not only to mechanical manipulation but also to vascular disruption of the quadrigeminal plate at the tumor resection. Postoperative neurologic deterioration may be due to hemorrhage in the tumor resection cavity or other intracranial compartment, cerebral or cerebellar swelling, or acute hydrocephalus. When the third ventricle is manipulated, one should carefully monitor the serum sodium level and urinary output to detect an inappropriate secretion of antidiuretic hormone or diabetes insipidus.

The true frequency of venous infarcts in the thalamus and basal ganglia secondary to surgical occlusion of the vein of Galen or its tributaries is not known. It is known that there is extensive collateral circulation in the vein of Galen and its tributaries. The consequences of surgical occlusion of the galenic system may have been overstated,^{66,73} but one should try to preserve these deep veins. Intraoperative hemorrhage from the vein of Galen is usually controlled by the application of hemostatic agents and gentle compression with a cottonoid.

39.8 Adjuvant Therapies

39.8.1 Germ Cell Tumors

Among germ cell tumors, teratomas, either mature or immature, necessitate surgical removal because of their lack of response to adjuvant therapy. Once a mature teratoma is removed, the cure rate is extremely high without further therapy. Other tumors (germinomas and NGGCTs), however, need further therapy. They have shown sensitivity to RT and chemotherapy, and these adjuvant therapies have become the primary form of the treatment.

Irradiation

The radiosensitivity of germinomas has been well recognized. Total eradication of the tumor can be achieved with only 1,600 cGy of radiation.⁷⁴ After treatment with RT alone for biopsy-proven pineal germinomas, the rate of 5- to 15-year disease-free survival is 80 to 100%.^{21,43,44,75,76}

The doses of irradiation for pineal germinomas have been controversial. The doses of irradiation to the brain for germinomas generally range from 5,000 to 5,500 cGy in the literature.⁷⁷ Some authors contend that the dose should be lowered for this radiosensitive tumor. Comparative disease-free survival rates were achieved with a dose to the primary tumor site of less

than 4,800 cGy,^{78,79} while others report that even in patients with multifocal germinomas treated with 3,000 cGy to the whole ventricle, tumor control was excellent.⁸⁰

The question of whether the field of irradiation should be limited to the primary tumor site and its margin^{77,79} or should include the whole brain or ventricle^{21,31,76,80} or the craniospinal axis^{43,81} has been controversial. Some recommend stereotactic irradiation or brachytherapy because these conformal irradiation techniques would improve efficacy and reduce radiation risks.⁸² The reported incidence of CSF dissemination of intracranial germinomas in the literature range from 10⁸ to 52%.⁵² For localized germinomas, it is accepted that irradiation should be applied to the whole ventricle or to the craniospinal axis when there is evidence of CSF dissemination.^{52,77,83} Lafay-Cousin et al attained excellent responses in bifocal germinomas with chemotherapy followed by whole-ventricle RT.⁸⁴ The risk for recurrence of germinomas in the leptomeninges without prior irradiation to the spine is in the range of 6 to 20%,^{21,76,85} whereas Wolden et al reported the spine-only failure rate to be only 2%.⁴⁴ In the previous trial (Children's Oncology Group [COG] ACNS0232), germinomas were treated with 2,100 cGy to the whole ventricle and a 2,400-cGy boost to the primary site; the radiation dose to the primary site was decreased to 3,000 cGy when neoadjuvant chemotherapy was used, and a complete response was attained. In a current clinical trial in the United States (COG ACNS1123), patients with pure germinomas receive 1,800 cGy to the whole ventricle with a 1,200-cGy boost to the tumor bed following chemotherapy if they are complete responders; patients with a partial response receive 2,400 cGy to the whole ventricle and a 1,200-cGy boost to measurable disease sites.

The younger the patient and the greater the dose and field of the irradiation, the greater the sequelae of ionizing irradiation to the developing central nervous system. Intellectual retardation and endocrine dysfunction are relatively common sequelae, occurring in approximately 25%, after irradiation for pineal germinomas in childhood.⁸⁶ However, Merchant et al reported no significant differences between the pre- and postirradiation IQs of children with intracranial germinomas who received craniospinal axis irradiation with a median dose of 2,560 cGy.⁸¹

Despite their high sensitivity to radiation, about 10% of germinomas show recurrence. Relapse may be due to an inadequate initial radiation field, the growth of a radiation-resistant tumor component, such as teratoma or NGGCT, or shunt-related extraneural metastases.⁸⁷ Among germinomas, those associated with an elevated β -HCG level (>50 IU/L) may be less sensitive to radiation than pure germinomas.^{21,88}

Contrary to the successful results of RT in germinomas, the response to RT alone in NGGCTs has been poor. The 5-year survival rate after RT ranges from 10 to 27%²¹ to 60%.⁴⁴ The Japanese Intracranial Germ Cell Tumors Study Group reported a median survival time of 18 months and a rate of CSF dissemination or hematogenous dissemination of 45% among patients with NGGCTs.²¹ The same report showed that patients who had pure choriocarcinoma, yolk sac tumor, or embryonal cell carcinoma had a 5-year survival rate of 9.3%, whereas patients who had germinomas mixed with elevated β -HCG or teratoma, immature teratoma, or mixed tumors consisting predominantly of germinoma or teratoma had a 5-year survival rate of 70%. A few centers reported the value of radiosurgery for malignant germ

cell tumors. There were diverse responses to radiosurgery among patients with malignant germ cell tumors.^{89,90}

Chemotherapy

The sensitivity of germ cell tumors to chemotherapy has been well recognized. Allen et al⁹¹ and Kobayashi et al⁹² reported a high response rate among germ cell tumors to neoadjuvant multiple-agent chemotherapy. Subsequently, multiple reports indicated high response rates of malignant germ cell tumors to neoadjuvant chemotherapy.^{75,93,94} In 1994, Allen et al reported a 100% response rate of germinomas to single-agent chemotherapy with carboplatin in 10 patients.⁹⁵

A European prospective study using multiple-agent chemotherapy in 1996 showed high response rates among both germinomas and NGGCTs. The rates of complete response to the chemotherapy did not differ between the germinoma group (84%) and the NGGCT group (78%).⁴⁰ Also, the Japanese Pediatric Brain Tumor Study Group reported in 2001 similarly high rates of responses among germinomas following multiple-agent chemotherapy consisting of etoposide with carboplatin or cisplatin.⁹⁶ Complete response rates were 83.6% among patients with germinoma and 77.8% among those with germinoma with syncytiotrophoblastic giant cells, whereas patients with NGGCT showed no or limited responses.⁹⁶

However, despite the high early response rates, both studies reported that subsequent follow-up without RT showed high rates of recurrence. The European study showed recurrences in 28 (51%) of the 55 patients with a complete response to neoadjuvant chemotherapy, which occurred between 8 and 49 months.⁴⁰ In this study, age of the patient, tumor location, presence of CSF dissemination, extent of tumor resection, and positivity for tumor markers did not influence outcome. However, a statistically significant difference was noted between the pathologic types: the 5-year survival rates were 84% for the germinoma group and 62% for the NGGCT group.

Similarly, the Japanese study showed a 50% recurrence rate within 1.5 years among patients with germinomas who had an initial complete response.⁹⁶ Most recurrences in the European study were treated with a combination of RT and chemotherapy. Notably, all 10 patients who received cyclophosphamide for recurrence showed a complete response. Although 10% (7 of 71 patients) died of the toxic effects of chemotherapy, this study clearly showed the chemosensitivity of these tumors, resulting in at least short-term remission.

A COG protocol (ACNS0122) treated NGGCTs with neoadjuvant chemotherapy, with the diagnosis confirmed based upon the results of testing for tumor markers or biopsy. Following two to three cycles of chemotherapy and an evaluation of the responses of the tumor markers or the responses on neuroimaging, second-look surgery was recommended if there was any concern for residual tumors. At second-look surgery, tumors resistant to radiation, such as mature or immature teratomas, may be encountered. These teratomas are also chemoresistant and may continue to grow during or after chemotherapy. Growing teratomas require surgical resection.⁹⁷ These patients subsequently received RT with 5,400 cGy to the tumor sites and 3,600 cGy to the craniospinal axis. Craniospinal irradiation remains controversial. In the latest

COG protocol (ACNS1123) for localized germ cell tumors, patients receive 3,060 cGy to the whole ventricle and a 2,340-cGy boost to the primary tumor site if the tumors respond to chemotherapy.

Chemotherapy is effective not only for primary tumors but also for disseminated germinomas. In patients who received a CSF diversion shunt for malignant germ cell tumor, chemotherapy would effectively reduce the possibility of peritoneal spread of the tumor cells.

A high response rate of NGGCTs after multiple-agent chemotherapy has been reported.⁹⁸ In a recent report from the COG regarding the use of multiple-agent induction chemotherapy among children with NGGCTs (COG ACNS0122), 32% achieved a complete response and 21.5% achieved a partial response (S. Goldman, personal communication, 2012). Certain malignant NGGCTs are extremely vascular. These tumors can be treated initially with chemotherapy, which not only reduces the size of the mass but also reduces the vascularity of the tumor. Second-look surgery for residual tumor after neoadjuvant chemotherapy is recommended before further treatment.⁴⁰ The residual tissues resected at second-look surgery after chemotherapy are often resistant to radiation, such as teratoma or necrotic tissue without viable tumor cells.⁹⁹ Of the 19 patients treated in COG ACNS0122, 13 were found to have teratomas, 4 fibrosis, and 4 persistent NGGCT. Paradoxical acceleration of the growth of mature teratomas (growing teratoma syndrome) may occur following neoadjuvant chemotherapy.^{97,100} The dose and field of irradiation may be reduced following chemotherapy.^{21,101} A combination with chemotherapy and a reduced dose of irradiation with local fields showed increased cure rates and reduced radiation-induced side effects, including anterior pituitary dysfunction.^{101–103}

39.8.2 Pineal Parenchymal Tumors

Pineoblastomas frequently affect infants and young children. They tend to recur and disseminate without appropriate therapy.^{4,10,16,53} Pineocytomas, however, are considered to be benign, and surgical excision can lead to a cure of affected patients.¹⁰⁵

Patients with pineoblastoma are treated with adjuvant therapy. For very young children, postoperative adjuvant chemotherapy was used in both a Pediatric Oncology Group (POG) and a Children's Cancer Group (CCG) study. The former included 11 patients younger than 3 years who received combination chemotherapy ("Baby POG") with cyclophosphamide, vincristine, cisplatin, and etoposide.⁵³ None of these children underwent gross total resection of tumor. All children ultimately failed chemotherapy between 2 and 11 months. The sites of relapse were frequently in the primary pineal location and in the CSF. No patient with leptomeningeal spread responded to chemotherapy. The CCG treated eight infants younger than 18 months of age at diagnosis with an eight-drugs-in-one-day (8-in-1) chemotherapy regimen.¹⁰⁶ All patients showed progressive disease at a median of 4 months from the start of treatment. Mandera et al treated 10 children with pineoblastoma with resection and chemotherapy and reported a mean survival time of 24.7 months and a 3-year survival rate of only 36%.^{2,6} On the other hand, the group of patients who were older than 18 months

of age and received craniospinal RT and chemotherapy had better survival. These patients had a 3-year progression-free survival rate of 61%, which was better than that for children with other supratentorial PNETs. According to Ashley et al, children with pineoblastoma responded to some degree to postoperative high-dose cyclophosphamide therapy.¹⁰⁷ However, cyclophosphamide therapy for recurrent pineoblastomas was not effective. A report from Duke University on the use of high-dose chemotherapy with autologous stem cell rescue followed by RT showed promising survival data, with 4-year progression-free and overall survival rates of 69% and 71%, respectively.¹⁰⁸

The value of aggressive total resection of pineoblastoma remains an enigma. Some recommend no further resection once biopsy confirms pineoblastoma.¹⁰⁶ Anecdotal long-term survival after biopsy and RT was reported.^{109,110} Gross total resection of other PNETs, medulloblastomas in particular, has been considered to provide better patient outcome. However, despite similar therapeutic modality, the prognosis of children with pineoblastoma and other supratentorial PNETs remains worse than the prognosis for those with medulloblastoma.¹¹¹ The extent of tumor resection may show a trend toward an association with outcome, with better survival following maximum tumor resection than after partial resection, but it did not show statistical differences in patient outcome.^{16,106}

Pineocytomas with a pineoblastic component are regarded as malignant and treated accordingly. However, pineocytomas are in general considered to be benign and rarely disseminate.¹⁴ Mandera et al reported that only 2 of 16 children with pineocytoma had recurrence after resection alone.^{2,6} However, some authors consider pineocytoma a malignant tumor and recommend RT,^{112,113} whereas others doubt the effects of RT on pineocytomas.¹¹⁰ The lack of responsiveness to radiation was noted by Vaquero et al, who observed that pineocytomas show little or no response to so-called diagnostic RT at a dose of 2,000 cGy.¹¹⁴ However, radiosurgery is considered to be more effective, and Hasegawa et al reported a 100% local control rate.¹¹⁵ None of the patients reported by Vaquero et al had tumor recurrence after surgical resection without further adjuvant therapy.

39.8.3 Astrocytomas

Benign astrocytomas in the pineal region arise in the quadrigeminal plate, tegmentum of the midbrain, or posterior thalamus. Superior vermian astrocytomas may extend to the pineal region, and advanced neuroimaging studies disclose the origin of the tumor. A majority are juvenile pilocytic astrocytomas. They are often well demarcated but do not possess an obvious tumor capsule. However, direct surgical resection may be associated with postoperative morbidity.

Astrocytomas of the quadrigeminal plate usually present with indolent progression. They are often managed with CSF diversion alone.¹¹⁶⁻¹¹⁸ Progression of disease characterized by enlargement of the tumor was noted in 25% of patients during follow-up after placement of a CSF diversion shunt. When disease progression occurs, biopsy (open or

stereotactic) followed by local irradiation provides long-term survival.¹¹⁶

39.9 Management Protocols

Neuroimaging studies, both CT and MR imaging, should be carefully reviewed and their findings correlated with patient's age, sex, presenting symptoms, and tumor markers. The presence or absence of hydrocephalus should be determined. If hydrocephalus is the presenting sign, immediate medical attention is needed. Placement of a ventriculoperitoneal shunt is avoided if possible because of concerns about CSF seeding and the development of shunt dependency and slit ventricles. One option is ETV (with CSF for tumor markers and cytology obtained at the same time), and another is craniotomy with tumor resection to restore the CSF pathway.

39.9.1 Tumors of the Pineal Gland

In children and adolescents with pineal region tumors, the serum and CSF should be evaluated for tumor markers (AFP and β -HCG) to rule out NGGCT. Neuroimaging studies often enable the differentiation of pineal teratomas (mature or immature) from other tumors because of their distinct characteristic appearance. Neuroimaging studies are also often diagnostic for pineal germinomas in male teenagers when testing is negative for tumor markers. When testing for tumor markers is negative, surgical biopsy is indicated. Neuroendoscopic biopsy at the time of ETV has become widely accepted. When testing for tumor markers is positive, neoadjuvant chemotherapy is recommended without surgical biopsy. After initial chemotherapy, it is advised that these patients undergo a second-look operation for radiographically defined residual tumor. After the second-look operation, RT is applied depending on the results of histologic examination and testing for tumor markers. Solid double tumors in both the anterior and posterior third ventricle are considered to be malignant germ cell tumors (germinomas if the testing for markers is negative, otherwise NGGCT) and require chemotherapy followed by RT.

Germ cell tumors among infants and preschool children are rare. The most common tumor of pineal origin at this age is pineoblastoma or atypical teratoid/rhabdoid tumor. These tumors require histologic confirmation, and tumor resection is advised before adjuvant therapy.

39.9.2 Tumors of the Quadrigeminal Plate or Thalamic Origin

Hydrocephalus, if present, is treated with ETV. If the lesion is small and intrinsic, it can be followed closely with MR imaging. When tumor progression is confirmed, surgical resection may be advised. However, if the lesion is large, contrast-enhancing, or largely cystic, a craniotomy is indicated, and histologic diagnosis needs to be confirmed. For benign astrocytomas, once adequate tumor resection is accomplished, further follow-up is recommended. However, unresectable, progressive astrocytoma is treated with chemotherapy and/or RT.

Pearls

In this author's experience:

1. The histologic nature of a pineal region tumor of childhood is often predictable based on the sex, age, neuroimaging appearance, and tumor markers. However, if there is any doubt, one should confirm histology by means of ventriculotomy, stereotactic biopsy, or open craniotomy.
2. Hydrocephalus is the primary cause of symptoms. It is treated by endoscopic third ventriculostomy, when the CSF studies such as cytology and tumor markers are done.
3. Germinomas and most NGGCTs are chemosensitive. Neoadjuvant chemotherapy should be incorporated in the treatment protocol.
4. Pineal region tumors can be removed with minimum morbidity through supratentorial or posterior fossa approaches. Surgeons should be familiar with advantages and disadvantages of both approaches.

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40 Medulloblastomas

Vijay Ramaswamy and Michael Taylor

Medulloblastomas are embryonal tumors arising from the cerebellum, initially described by Bailey and Cushing in 1925. Medulloblastoma is the most common malignant brain tumor of childhood, occurring at an incidence of 0.73 per 100,000 person-years and comprising approximately 25% of all pediatric brain tumors.¹ Medulloblastoma can occur in all age groups; however, it is most common in children younger than 9 years of age, and the incidence decreases with increasing age thereafter. There exists a modest male preponderance in a ratio of 1.4:1, which is most notable in children younger than age 4. In the past, medulloblastoma was classified as a primitive neuroectodermal tumor (PNET); however, recent data have shown that medulloblastoma is biologically distinct from other intracranial PNETs, specifically supratentorial PNETs, pineoblastoma, and brainstem PNETs. As such, medulloblastoma is considered a disease distinct from other intracranial PNETs. Recent advances over the past 20 years have significantly improved our understanding of the biology of medulloblastoma, and advances in chemotherapy and radiation therapy have significantly improved outcomes.

40.1 Clinical Presentation

The clinical signs and symptoms of medulloblastoma are usually related to hydrocephalus secondary to obstruction of the fourth ventricle. Most tumors are diagnosed when they are quite large and obstruct the flow of cerebrospinal fluid (CSF) in the fourth ventricle; before this, most either are asymptomatic or cause subtle clinical symptoms. Almost all children with medulloblastoma present with symptoms of increased intracranial pressure, specifically early morning vomiting and headache. The common sequence of events is early morning headache relieved by vomiting and resolution of symptoms. As the tumor progresses, the diurnal variation of the headache and vomiting tends to become less pronounced, and these symptoms are more constant. Truncal ataxia and diplopia secondary to sixth nerve palsy are also common presenting features in addition to vomiting and headache.² More lateral lesions may present with appendicular ataxia and occasionally focal weakness. Other neurologic symptoms localizing to the posterior fossa and brainstem can be present at diagnosis; however, they are much less common. Seizures rarely occur in children with medulloblastoma, and it is much more common for decerebrate posturing to be misinterpreted as tonic seizure. The time to diagnosis varies; however, children typically present acutely, and only rarely do children have a prediagnostic interval of longer than 2 months. It is not uncommon for children to undergo a gastrointestinal work-up before diagnosis. However, longer times to diagnosis do not correlate with reduced survival or worse neurologic outcome.³ The differential diagnosis for medulloblastoma at presentation includes ependymoma, pilocytic astrocytoma, atypical teratoid/rhabdoid tumor (AT/RT), and embryonal tumor with abundant neuropil and true rosettes (ETANTR). It can be difficult to distinguish these entities based on clinical symptoms alone, although children with pilocytic astrocytomas tend to have a longer duration of symptoms, and children with

ependymomas have a history of neck pain or stiffness with associated torticollis due to caudal invasion of the tumor through the foramen magnum.

Infants and very young children tend to have slightly different clinical presentations. Owing to their open sutures, infants present with macrocephaly and a head circumference that crosses percentiles. Infants with open sutures may present with irritability, lethargy, bulging fontanel, downward gaze due to pressure on the pretectum, and developmental arrest or regression. Very young children also tend to present with more catastrophic symptoms of hydrocephalus, such as apnea, bradycardia, and loss of consciousness, because of a more advanced stage of disease at diagnosis secondary to an increased tolerance of hydrocephalus. Adults commonly present with atypical symptoms and a longer prediagnostic interval because of a higher incidence of desmoplastic disease, which can arise in more lateral regions of the cerebellum. For example, patients who have cerebellopontine angle lesions present with vertigo, vomiting, nystagmus, and diplopia, which can be mistaken for vestibular canal symptomatology.

Metastatic disease is present in 40% of patients at diagnosis and is commonly asymptomatic; however, metastases may present with symptoms of nerve root involvement or spinal cord symptoms. Recurrent disease is rarely diagnosed clinically; rather, it is diagnosed on routine serial neuroimaging, and the likelihood of recurrence decreases with time.

Medulloblastoma can be associated with several familial cancer syndromes, specifically Gorlin syndrome, Turcot syndrome and Li-Fraumeni syndrome.⁴ Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is present in 1 to 2% of patients with medulloblastoma and is an autosomal-dominant disorder associated with germline mutations in the *PTCH* gene on 9q31. The major criteria are multiple (more than two) basal cell carcinomas, jaw cysts (keratocysts) or bone cysts, palmar or plantar pits (more than three), early calcification of the falx cerebri, and a first-degree relative with Gorlin syndrome. Minor criteria include congenital skeletal abnormalities: specifically, rib abnormalities or fused vertebrae, macrocephaly, cardiac or ovarian fibroma, medulloblastoma, lymphomesenteric cysts, and various congenital malformations. Medulloblastoma in Gorlin syndrome usually develops before 2 years of age and is usually of desmoplastic histology and of the sonic hedgehog (SHH) subgroup. The outcome in these patients is more favorable than in those with sporadic medulloblastoma; however, basal cell carcinoma frequently develops in the irradiated skin, and these patients should be monitored on a long-term basis. Another germline mutation in the SHH pathway is *hSUFU*, which also leads to desmoplastic medulloblastoma but does not have the other manifestations seen in Gorlin syndrome.^{5,6} Turcot syndrome comprises distinct disorders: multiple colorectal neoplasms and tumors of the central nervous system (astrocytoma, medulloblastoma, pineoblastoma, ganglioglioma, ependymoma, glioblastoma). Medulloblastoma in patients with Turcot syndrome typically occurs before the age of 10 years and is not clinically different from sporadic disease. Turcot syndrome in medulloblastoma is associated with germline mutations in the adenomatous polyposis coli gene (*APC*) on 5q21. Li-Fraumeni syndrome is an autosomal-dominant disorder secondary to

germline missense mutations in the *TP53* gene on 17p13. Li-Fraumeni syndrome can lead to multiple different tumors, of which breast cancer, osteosarcoma, and brain tumors are the most common. Medulloblastoma occurs in approximately 5% of patients with Li-Fraumeni syndrome. Any patient with medulloblastoma and a strong family history of brain tumors or a previous history of an extraneural tumor warrants investigation for a germline *TP53* mutation and should be monitored on a lifelong basis for the development of other tumors. More rare familial syndromes associated with medulloblastoma include Bloom syndrome and Fanconi anemia. Bloom syndrome is an autosomal-recessive disorder characterized by dwarfism, sun sensitivity, and a characteristic facial appearance. It is more common in Ashkenazi Jews and is secondary to a mutation in the *BLM1* gene (RecQ protein-like-3) on 15q26.1. Fanconi anemia is an autosomal-recessive disorder that predisposes to bone marrow failure and leukemia and is secondary to several Fanconi anemia susceptibility genes.

40.2 Diagnostic Work-up

The initial diagnosis of medulloblastoma is usually made with noncontrast computed tomography (CT) followed by magnetic resonance (MR) imaging. On a noncontrast CT scan, a medullo-

blastoma is typically a hyperattenuating midline mass surrounded by vasogenic edema; it enhances homogeneously following the administration of contrast (► Fig. 40.1).⁷ The majority of lateral cerebellar medulloblastomas are of desmoplastic histology (► Fig. 40.2). Hydrocephalus is present on initial CT in over 95% of patients. The findings on CT are not specific for medulloblastoma and cannot reliably be distinguished from those of ependymoma or AT/RT. MR imaging with gadolinium enhancement is the preferred method for the initial evaluation of posterior fossa tumors. Younger children require general anesthesia for image acquisition, and care should be taken in these instances because there is a risk for respiratory depression. When sedation is indicated, it should be administered by a pediatric anesthesiologist. On T1-weighted MR imaging, medulloblastomas are hypointense or isointense relative to gray matter and become hyperintense with the administration of gadolinium. On T2-weighted imaging, the signal is variable and can be hyperintense to hypointense relative to gray matter. Diffusion-weighted imaging can be very useful in discriminating medulloblastoma from ependymoma or astrocytoma (► Fig. 40.3). Because medulloblastomas consist of dense small round cells with minimal cytoplasm and reduced free water, they exhibit diffusion restriction with a reduced apparent diffusion coefficient.

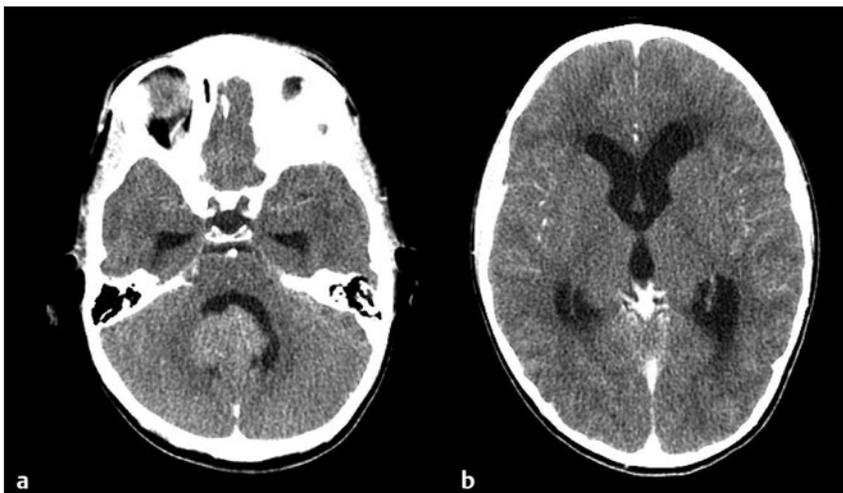


Fig. 40.1 Contrast-enhanced computed tomographic scan through the (a) posterior fossa and (b) third ventricle. Note the significant triventricular hydrocephalus at diagnosis.

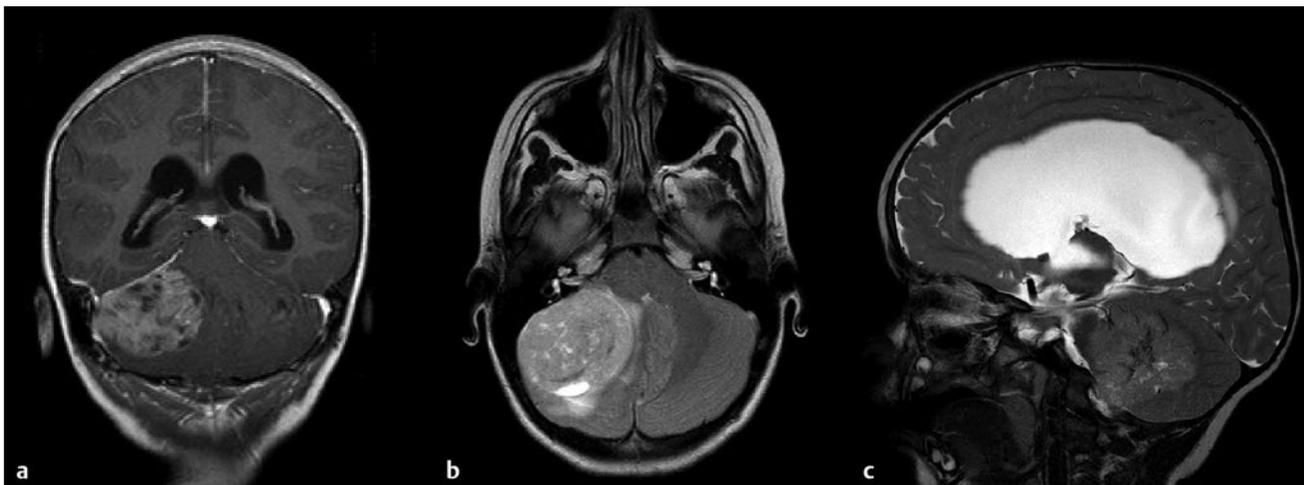


Fig. 40.2 (a) Coronal T1-weighted gadolinium-enhanced MRI. (b) Axial T2-weighted MRI. (c) Sagittal T2-weighted MRI showing a lateral desmoplastic tumor, commonly seen with the sonic hedgehog subgroup.

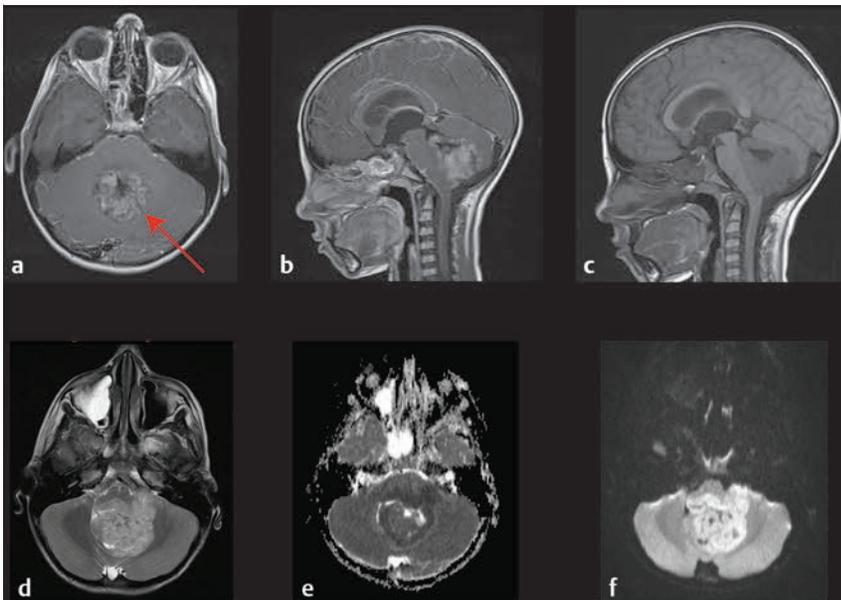


Fig. 40.3 Magnetic resonance (MR) image at diagnosis of a midline medulloblastoma. (a) Axial and (b) sagittal T1-weighted gadolinium-enhanced MR images. Note the homogeneous enhancement following contrast administration. (c) Sagittal T1-weighted unenhanced MR image. (d) Axial T2-weighted MR image (note the peritumoral edema). (e) Axial apparent diffusion coefficient (ADC) map and (f) axial diffusion-weighted Image (b1000). Note the restricted diffusion observed throughout the tumor.

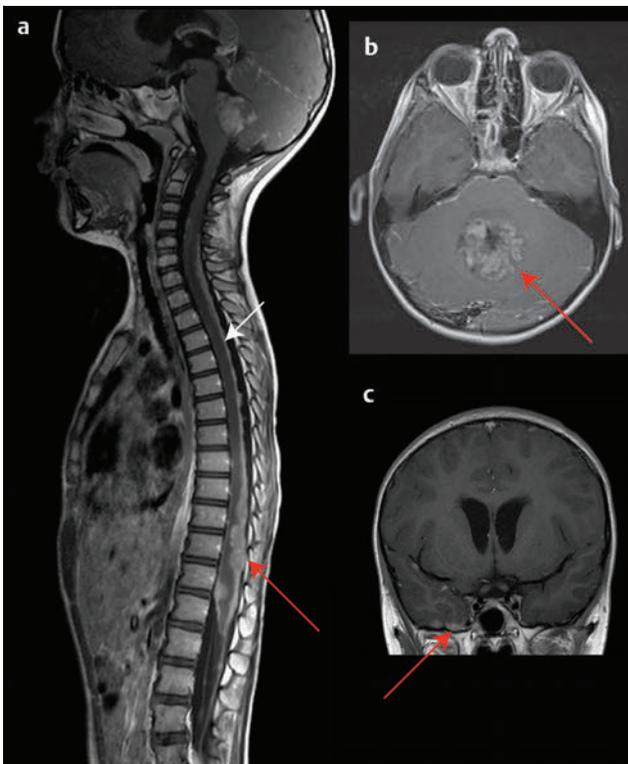


Fig. 40.4 Metastatic medulloblastoma. (a) Sagittal T1-weighted gadolinium-enhanced magnetic resonance (MR) image of the entire spinal cord showing diffuse nodular (red arrow) leptomeningeal metastases throughout the entire spine. (b) Sagittal T1-weighted gadolinium-enhanced MR image of the lower thoracic and lumbar spinal cord showing a classic "sugar coating" pattern of laminar metastases (white arrow) covering the spinal leptomeninges. (c) Coronal T1-weighted gadolinium-enhanced MR image showing supratentorial nodular metastases (red arrow) along the inferior surface of the right temporal lobe.

This is in contrast to ependymomas and pilocytic astrocytomas, which typically do not have restricted diffusion.⁸ AT/RTs also display restricted diffusion; however, young age of the patient, cerebellopontine angle involvement, and intratumoral hemorrhage can help distinguish AT/RTs from medulloblastomas radiologically.⁹ When feasible, preoperative imaging of the entire craniospinal axis is desirable for adequate staging of disease because 40% of medulloblastomas are metastatic at diagnosis (► Fig. 40.4). However, imaging of the entire craniospinal axis should be performed 2 weeks or later postoperatively for full staging to avoid the possibility of false-positives due to debris and blood products.¹⁰ Cranial MR imaging should also be repeated within 72 hours postoperatively or after 2 weeks postoperatively because residual tumor of more than 1.5 cm² may be correlated with a higher risk for disease.¹¹ Cranial MR imaging performed between 3 and 14 days postoperatively can be falsely positive because of the presence of blood products and debris. Ultimately, pathologic diagnosis is required for a firm diagnosis.

Lumbar CSF sampling is also warranted in every patient with a new diagnosis of medulloblastoma. Lumbar sampling is preferred over ventricular sampling at surgery or through a shunt because lumbar CSF sampling is more sensitive than ventricular sampling.^{12,13} Ideally, both ventricular CSF sampling at surgery and lumbar CSF sampling 2 weeks postoperatively should be obtained because there are cases of discordance between the two sites, and positive ventricular CSF cytology intraoperatively has been associated with a poorer outcome.^{13,14} Spinal MR imaging is not a substitute for lumbar CSF sampling and vice versa because up to 18% of cases of leptomeningeal disease can be missed if only one of the two modalities is used.¹⁵

There are a paucity of data regarding the role of bone marrow sampling at diagnosis; however, routine extraneural staging is not warranted because extra neural disease is extremely uncommon at diagnosis. If there is suspicion of extraneural disease, FDG-PET (fluorodeoxyglucose F 18 positron emission tomography) and bone marrow biopsy are the preferred modalities. Bone marrow sampling should be considered if the

child will be undergoing autologous stem cell harvest as part of the treatment regimen. Extraneural disease is more commonly present at recurrence, particularly very late recurrences, and can be present in the absence of intracranial disease.¹⁶ Hearing and creatinine clearance should be evaluated postoperatively in all patients before the initiation of either radiation therapy or chemotherapy because both platinum-based chemotherapy and radiotherapy are ototoxic and nephrotoxic.

40.3 Hydrocephalus

The majority of patients with medulloblastoma present with hydrocephalus due to obstruction of the fourth ventricle. As such, the management of hydrocephalus is usually the first intervention. Most patients can be managed with preoperative dexamethasone (0.45 mg/kg per day divided into three doses, with an initial dose of 0.45 mg/kg), which results in significant alleviation of the symptoms and a reduction in vomiting. Placement of an extraventricular drain (EVD) preoperatively is occasionally necessary; however, in instances in which hydrocephalus is resulting in cardiopulmonary instability and/or in cases of impending herniation, it is warranted as a tempering measure until resection can take place. When an EVD is placed, consideration must be given to the possibility of upward herniation, and the rate and quantity of CSF drainage must be carefully monitored. The height of an EVD can be gradually increased in the postoperative period, and in most cases the EVD can be successfully removed within a week to 10 days postoperatively. From 10 to 40% of children require permanent CSF diversion postoperatively, and as such, routine ventriculoperitoneal shunting is not indicated perioperatively. The need for shunting is greatest in young children and in those with very large ventricles at diagnosis, more extensive tumors, and metastatic disease.¹⁷ CSF diversion is rarely required in children older than age 10. When persistent hydrocephalus is present, either ventriculoperitoneal shunting or endoscopic third ventriculostomy can be considered.¹⁸ Several series have reported high success rates with endoscopic third ventriculostomy for persistent hydrocephalus, and it should be considered in patients requiring postoperative shunting who are suitable candidates for this procedure. There is limited evidence for the use of routine endoscopic third ventriculostomy in all patients because a significant proportion of patients do not have persistent hydrocephalus.¹⁸ Rare cases of peritoneal seeding of medulloblastoma through ventriculoperitoneal shunts have been described.¹⁹

40.4 Tumor Resection

Gross total resection of the primary posterior fossa mass through a suboccipital craniotomy is the most common initial treatment for medulloblastoma. The goal of surgical resection is to achieve a gross total resection or, if this is not possible, to resect as much of the tumor as is safely possible. There is seldom any role for a limited biopsy. The craniotomy is performed with the patient in the prone position and the neck flexed. Once the superficial tissues and muscles are dissected, a portion of the occipital bone and the lamina of C1 are removed. The dura covering the cerebellum is then opened, and the two hemispheres are retracted through either the split vermis or a telovelar

approach. Although medulloblastoma rarely invades the floor of the fourth ventricle, it is important to visualize the floor of the fourth ventricle at the onset of the surgery to ensure that the resection is not carried into the brainstem. Severe cranial nerve palsies can result if the surgeon aggressively resects tumor that invades the brainstem, and this is never indicated because the tumor is sensitive to both chemotherapy and radiation, and residual brainstem disease likely does not significantly alter outcome.¹¹ If the tumor invades the cerebellopontine angle, then the use of intraoperative brainstem auditory evoked potentials can be considered. Medulloblastomas can be fairly vascular, leading to considerable hemorrhage intraoperatively, and care should be taken to prevent blood loss, particularly in young children. Dural closure should be achieved in a watertight fashion and the bone replaced after the procedure has been performed. Postoperative MR imaging should be performed to determine the extent of resection within 72 hours of surgery so as to avoid obscuration by blood products and gliosis. Residual disease over 1.5 cm² is possibly associated with poorer outcome, and repeated resection for large residual tumor should be considered unless the surgeon stopped the initial resection because of excessive vascularity or invasion of critical structures.¹¹

40.5 Pathology

The definitive diagnosis of medulloblastoma is made on microscopic pathologic examination. On gross examination, medulloblastoma appears as a pinkish gray to purple mass with a clear interface separating it from normal cerebellum. In the operating room, it also appears as a highly vascular lesion owing to its blood supply principally from the posterior inferior cerebellar artery. Leptomeningeal metastases may be seen at the time of surgical resection as well, which appear as a whitish coating that resembles icing sugar. On microscopic examination, medulloblastoma appears as a “small round blue cell tumor” and is morphologically indistinguishable from supratentorial PNETs or pineoblastomas. Medulloblastomas are highly cellular and the cells are densely packed, with prominent nuclei and scant cytoplasm. A type of pseudorosette may be seen (Homer-Wright rosette) in which differentiated cells surround the neuropil. Histologically, there are three main types of medulloblastoma: (1) classic, (2) desmoplastic, and (3) large cell/anaplastic. Classic histology is by far the most common histology (>70%) and consists of sheets of small blue cells with densely packed isomorphic nuclei and a high proliferative index. Desmoplastic histology is more common in infants and adults and is most commonly associated with SHH pathway activation. Desmoplastic histology is characterized by nodules with a paucity of tumor cells surrounded by cells with a higher density, more pleomorphic nuclei, and densely packed reticulin fibers. Within the nodules, there is increased synaptophysin staining, and outside the nodules, there is a higher Ki-67 proliferation index, and the tumor cells are GFAP (glial fibrillary acidic protein)-positive. There is no consensus regarding how much desmoplasia is required to classify a tumor as desmoplastic. A variant of desmoplastic histology termed medulloblastoma with extensive nodularity (MBEN) is characterized by extensive nodularity and neuronal differentiation. The desmoplastic and MBEN variants in infants signified a favorable prognosis in several studies.²⁰ The large cell/anaplastic variant is aggressive and characterized

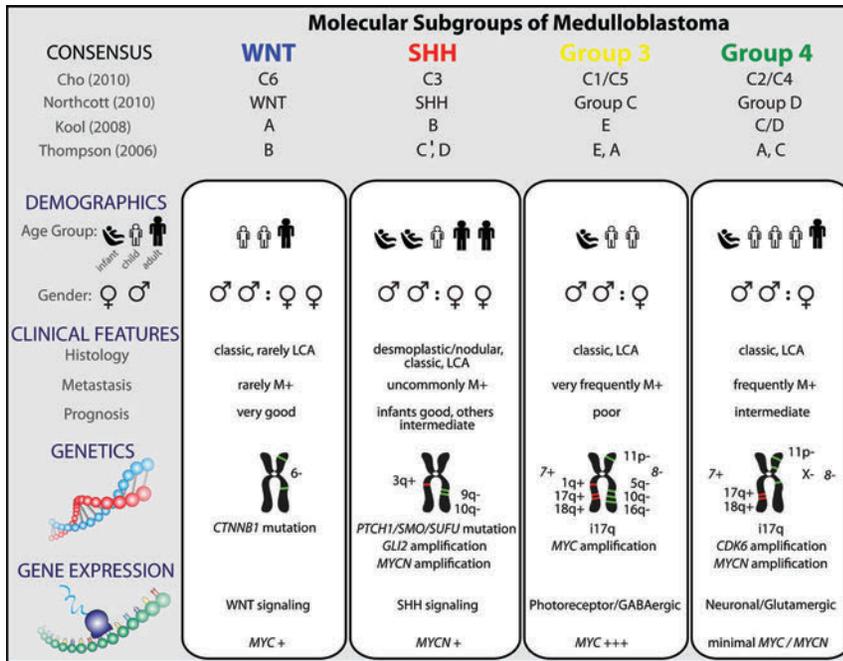


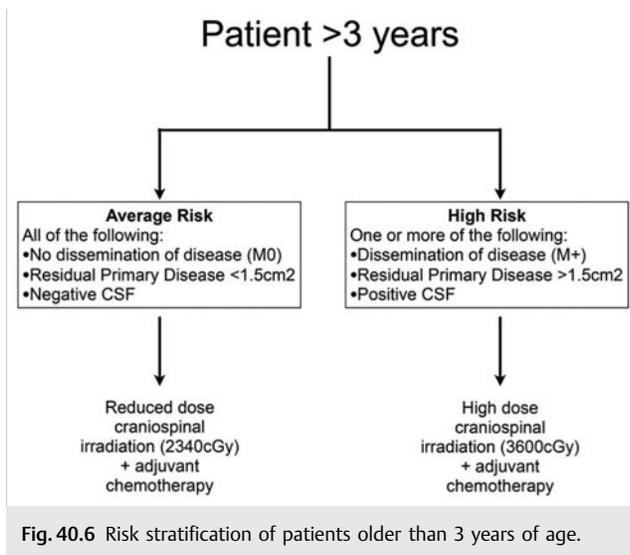
Fig. 40.5 Consensus molecular subgroups of medulloblastoma. Comparison of the various subgroups of medulloblastoma, including patient demographics, common genetic changes, and outcome. GABA, γ -aminobutyric acid; LCA, large cell/anaplastic; SHH, sonic hedgehog. (Used with permission from Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* 2012;123:467.)

histologically by large, irregular, and pleomorphic nuclei; circumscribed foci of necrosis; and apoptotic bodies. The large cell variant tends to have prominent nucleoli. The large cell/anaplastic variant accounts for approximately 4%, is more common in the group 3 molecular subgroup, is commonly associated with bulky spinal metastases at diagnosis, and has a poor prognosis. Pathologic variants include the medulloblastoma, which is characterized by a striated muscle component, and the melanotic medulloblastoma, which is characterized by a pigmented epithelial component forming tubules or clusters. Medulloblastomas are more commonly associated with isochromosome 17q, have frequent *MYC* amplification, and tend to be of large cell/anaplastic histology; however, because of a paucity of multicenter studies, their prognosis is indeterminate.²¹ Melanotic medulloblastoma is very rare, and its prognostic significance is unclear.

The pathologic differential diagnosis for medulloblastoma includes AT/RTs and ETANTRs. AT/RTs are most common in young infants and should be considered in any child younger than age 5 with medulloblastoma, or when a rhabdoid component is present on histologic examination. Molecularly, AT/RTs are characterized by loss of *INI1/hSNF5*. Therefore, INI1 immunoreactivity should be assessed in all infants in whom medulloblastoma is diagnosed; in AT/RTs, staining for INI1 will be negative in the tumor but positive in blood vessels, and in medulloblastoma, staining will be positive in both tumor and blood vessels. ETANTRs are rare tumors that can occur in any location, including the posterior fossa, and were previously called ependymoblastomas. ETANTRs are characterized molecularly by focal amplification of a microRNA cluster at the 19q13.42 locus and should be considered when the pathologic features include ependymoblastic rosettes and neuronal differentiation on a neuropil background.²² ETANTRs are found in young infants and portend a poor prognosis.

The advent of integrated genomics over the past 20 years has significantly advanced our understanding of the biology of

medulloblastoma. Several integrated genomic studies during the past 6 years have revealed that medulloblastoma comprises at least four variants, which are transcriptionally, genetically, and clinically distinct.^{23–25} These four subgroups are termed WNT, sonic hedgehog (SHH), group 3, and group 4 (► Fig. 40.5). The four molecular subgroups have significant prognostic value and predict survival independently of the presence of metastases or unfavorable histology. The WNT subgroup is characterized by activation of the WNT pathway, and tumors commonly harbor mutations in the β -catenin gene (*CTNNB1*). Patients with WNT-activated tumors, which occur primarily outside the infant age group, tend to have a very favorable prognosis.^{24,26} Patients with WNT-activated tumors are being considered for de-escalation of therapy in future clinical trial designs. The SHH subgroup is characterized by activation of the SHH pathway and is more common in infants with desmoplastic tumors and in adults; however, it can occur in all age groups and is associated with all histological variants. Infants with desmoplastic SHH-activated tumors have a favorable prognosis; however, other SHH-activated tumors have an intermediate prognosis. SHH pathway inhibitors such as smoothened inhibitors are currently in clinical trials and hold promise for personalized therapy in this subgroup of patients.²⁷ Group 3 medulloblastomas have a poor prognosis and are commonly associated with metastatic disease. *MYC* amplification is common in group 3 medulloblastomas, and the survival rate in these patients is dismal. Group 4 medulloblastomas have an intermediate prognosis and are commonly associated with isochromosome 17q and *MYCN* amplification. A molecular subgroup can be determined through several methods, including immunohistochemistry with a four-antibody method (DKK1 for WNT, SFRP1 for SHH, NPR3 for group 3, and KCNA1 for group 4) and gene expression profiling through either a whole transcriptome or a limited-gene approach.^{23,28} WNT subgroup medulloblastomas can also be diagnosed through nuclear immunoreactivity of β -catenin.²⁹ Other immunohistochemical approaches for the diagnosis of the four



subgroups include GAB1 immunoreactivity for SHH and negativity for YAP1 and filamin A for non-SHH/WNT. Markers of a poor prognosis for non-SHH/WNT subgroups include *FSTL5* overexpression, *MYC* amplification, *MYCN* amplification, and gain of chromosome 17q.^{24,30} *TP53* mutations have been suggested to portend a poor prognosis; however, the literature surrounding this is conflicting, including the observation that patients with *TP53* mutations in WNT-activated tumors have a good survival.^{31,32}

40.6 Staging and Outcome

The Chang system is the most commonly used staging system (see box “Chang Staging of Medulloblastoma (p.532)”). Children older than age 3 are categorized as having average-risk or high-risk disease based on the Chang staging system (► Fig. 40.6). The prognosis of patients with metastases does not differ for M1, M2, and M3.³³ A T-staging system of tumor invasiveness also exists; however, it is unclear whether this holds any prognostic value. All patients older than the age of 3 years with no evidence of disseminated disease and residual tumor at the primary site of less than 1.5 cm² are classified as having average-risk medulloblastoma. All patients younger than age 3 are designated as high-risk. Patients older than age 3 with average-risk disease have a 5-year survival rate of 85% with combined chemotherapy and reduced-dose radiotherapy, and patients older than age 3 with high-risk disease have a 5-year survival rate of 70% with combined chemotherapy and high-dose radiation therapy.^{26,34} In children younger than 3, histology is predictive of outcome; specifically, children with desmoplastic histology have a 2-year overall survival rate of 85%, compared with 34% for patients with other histologies.²⁰

Chang Staging of Medulloblastoma

- M stage
 - No evidence of tumor dissemination, with CSF negative for tumor cells
 - CSF positive for tumor cells

- Dissemination of disease into intracranial leptomeninges or lateral/third ventricle
- Dissemination of disease into intraspinal leptomeninges
- Dissemination of disease outside the central nervous system
- T stage
 - Tumor < 3 cm in diameter
 - Tumor > 3 cm in diameter
 - Tumor > 3 cm with spread to nearby structures
 - Tumor > 3 cm with spread into the brainstem
 - Tumor > 3 cm with rostral extension past the aqueduct of Sylvius or caudal extension past the foramen magnum

40.7 Nonsurgical Treatment

40.7.1 Radiation Therapy

Patients older than 3 years of age with average-risk disease are treated with reduced-dose (2,340 cGy) craniospinal irradiation, with a boost to the tumor bed or posterior fossa of 5,400 to 5,580 Gy after surgical resection of the primary tumor.^{26,34} Radiation therapy is followed by adjuvant, cisplatin-based chemotherapy in patients with average-risk disease and results in survivals of approximately 85% across several regimens.^{26,34} Radiation therapy is often given concomitantly with chemotherapy, typically vincristine. Patients who have high-risk disease are treated with 3,600 cGy of craniospinal irradiation, with a boost to the tumor bed and to focal metastases followed by adjuvant chemotherapy, resulting in survival of approximately 70%.²⁶ A delay of radiotherapy past 28 days postoperatively has a negative prognostic impact.³⁵ Chemotherapy with standard regimens before radiation has been investigated and results in inferior survival.³⁶ The role of hypofractionated radiotherapy is unclear; however, its use following chemotherapy can lead to good outcomes in high-risk disease.³⁷ Radiation therapy is associated with several adverse effects, particularly cognitive impairment, in younger children. Ototoxicity, thyroid dysfunction, growth failure, and radiation necrosis are frequently observed side effects of radiation therapy and are inversely correlated with age.^{38,39} The role of repeated irradiation for recurrent disease is unclear; however, a few studies have shown a benefit, specifically in focal recurrences, when repeated irradiation is combined with repeated resection.⁴⁰ Moreover, salvage radiotherapy for recurrent disease in infants treated with chemotherapy alone can significantly improve survival, particularly in those with local relapse.^{20,41,42} Children younger than age 3 have devastating cognitive outcomes when receiving craniospinal irradiation, and as such, protocols using chemotherapy alone are preferred despite inferior outcomes.³⁸

40.7.2 Chemotherapy

Current therapy for all patients with medulloblastoma includes chemotherapy. Children younger than age 3 are treated with chemotherapy-only approaches, even in cases of disseminated disease. Three approaches have been studied for infant medulloblastoma, including systemic induction chemotherapy, followed by myeloablative chemotherapy with autologous stem cell support, followed by radiotherapy for local relapse (Children’s Oncology Group [COG], Headstart, Société Française d’Oncologie Pédiatrique [SFOP]), combined systemic and intraventricular

chemotherapy (German Society for Pediatric Oncology and Hematology [GPOH]), and systemic chemotherapy with conformal local radiotherapy (United Kingdom, Children's Oncology Group).⁴² All three of these approaches result in similar 5-year overall survival rates of approximately 50 to 70%, with the desmoplastic variant having survivals close to 90%.⁴² The intraventricular methotrexate approach requires placement of an Ommaya catheter or a programmable shunt and adequate CSF flow. Intraventricular methotrexate should not be administered through a ventriculoperitoneal shunt without a device for transient occlusion to prevent methotrexate-induced peritonitis. Furthermore, intraventricular methotrexate is associated with a dose-dependent leukoencephalopathy of varying severity, and patients are at risk for radiation necrosis if they subsequently require radiation therapy. Young children treated with intrathecal methotrexate have a high risk for developing significant cognitive deficits, particularly in measures of intelligence and memory.⁴³ Patients older than age 3 with average-risk disease are treated with four to nine cycles of combination postirradiation adjuvant chemotherapy, which is usually cisplatin-based. Patients with high-risk disease have been treated with a variety of approaches; however, all these approaches administer adjuvant chemotherapy following high-dose craniospinal irradiation, with 5-year overall survival rates of approximately 70%.²⁶

Chemotherapeutic options for recurrent disease, particularly in children with prior irradiation, are limited. One potential option for recurrent disease is the use of high-dose chemotherapy with autologous stem cell support with or without repeated irradiation, which can result in long-term survival in 10 to 25% of patients.⁴⁴ However, these studies also suggest that the outcome is favorable only in those patients with no evidence of disease or minimal residual disease at the time of high-dose chemotherapy. Several agents are active against recurrent disease; however, there are very few long-term survivors, and the enrollment of patients with recurrent disease into a clinical trial is a reasonable option.

40.8 Complication: Posterior Fossa Syndrome

The most common postoperative complication is the posterior fossa syndrome, also referred to as cerebellar mutism or cerebellar affective syndrome. In a prospective Children's Cancer Group questionnaire-based study, approximately 22% of patients developed posterior fossa syndrome postoperatively; however, these cases were rated as moderate to severe, suggesting that the incidence of milder cases may be much higher.⁴⁵ The symptoms typically manifest 24 to 48 hours postoperatively.⁴⁶ Posterior fossa syndrome is characterized by a triad of (1) decreased production of speech or mutism, (2) cerebellar dysfunction including ataxia and axial hypotonia, and (3) neurobehavioral affective symptoms such as emotional lability, irritability, and apathy.^{47,48} The neurobehavioral symptoms can be the most distressing to families because children typically are inconsolable with sharp, high-pitched whining and display marked apathy with a lack of initiation and hypokinesia. Other symptoms, such as decreased oral intake and oromotor apraxia, have also been described with the syndrome.⁴⁸ Fecal and urinary incontinence has been observed in up to 60% of patients.⁴⁷ The pathophysiol-

ogy of posterior fossa syndrome is not completely known; however, there is evidence that perturbations in the proximal dento-thalamocortical pathway as a result of the midline tumor and/or surgical resection are causative.⁴⁹ Furthermore, there is increasing evidence pointing to the role of the cerebellum in speech initiation. Some studies have attempted to correlate tumor size with the development of posterior fossa syndrome; however, results of these studies have been inconclusive. There is also recent evidence of presurgical language impairment as a primary risk factor for development of the posterior fossa syndrome; children without a presurgical language deficit did not develop mutism, suggesting that the technical aspects of surgery are unlikely to be causative.⁵⁰ To this effect, surgical approaches that avoid splitting the cerebellar vermis do not seem to prevent development of the posterior fossa syndrome.^{47,48} The outcome of posterior fossa syndrome is variable. Typically, the child recovers from mutism at a mean of 8.3 weeks; however, a residual ataxic dysarthria is common. Indeed, speech impairments were present in 95% of patients with moderate or severe mutism 1 year postoperatively.⁴⁵ Other neuropsychiatric deficits are also noted in patients with posterior fossa syndrome, such as deficits in receptive language, memory impairment, cognitive function, and executive function, suggesting that multidisciplinary rehabilitation is required in these patients.^{45,48} There are no available modalities for either the treatment or prevention of posterior fossa syndrome that have been shown to be effective beyond the level of anecdotal reports. An intensive multidisciplinary rehabilitation program involving neurologists, physiatrists, and oncologists as well as speech, occupational, and physical therapists is required to manage the global neurologic dysfunction observed in these patients.

Pearls

- Pathologic diagnosis is necessary for all cases of medulloblastoma. Frozen tissue should be banked in all patients for molecular studies.
- Aggressive resection of brainstem infiltration is neither desired nor warranted; residual brainstem disease can be treated with radiation and/or chemotherapy and does not hold any negative prognostic value.
- A complete tumor staging work-up should be performed in every patient, including postoperative MR imaging of the entire neuroaxis and a lumbar CSF examination 2 weeks postoperatively.
- Radiation therapy in children older than age 3 should be initiated before 28 days postoperatively.
- Most children do not require postoperative ventriculoperitoneal shunting and can be successfully weaned from an extraventricular drain. Endoscopic third ventriculostomy should be considered in suitable candidates when CSF diversion is required.

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41 Ependymomas

Scott D. Wait, Michael Taylor, and Frederick A. Boop

Ependymoma is the third most common pediatric brain tumor, following medulloblastoma and astrocytoma in incidence. Pediatric neurosurgeons play an important role in treatment because ependymoma with gross total resection (GTR) have a high likelihood of cure, whereas those who do not fare poorly. Current standard therapy consists of GTR if possible, followed by local radiotherapy. Chemotherapy plays a less well-defined role in a minority of patients. Although many children with ependymoma are cured, a minority of children still die of this disease, illustrating the need for further clinical and basic science research on ependymomas.

41.1 Epidemiology, Clinical Presentation, and Pathogenesis

Neurosurgeons often speak of ependymomas as a homogeneous group of tumors despite several histologic variants, each with a distinct biology. Even among those tumors that are diagnosed as classic ependymomas on histopathology, there are several different types, again each with its own biology.^{1,2} Most current clinical and basic science studies deal with the ependymomas as a group, even though they diverge in regard to epidemiology, natural history, pathophysiology, and response to treatment.

The mean age at the diagnosis of pediatric ependymoma is 4 to 6 years, with about one-third of tumors diagnosed before the age of 3 years.³⁻⁷ Approximately 10% of pediatric brain tumors belong to the ependymoma group of tumors, comprising a much higher percentage than in the brain tumors of adults. Historical 5-year survival estimates range from 50 to 64%, with the progression-free survival (PFS) estimated rate lower, at 23 to 45%.^{6,8-11} In most cases, recurrence is found at the site of the original tumor, with isolated metastatic recurrence occurring in fewer than 20% of cases. Most children who have no evidence of disease at 5 years will be cured. The median time to recurrence is 13 to 25 months.^{32,69,74,76,83} Strikingly different from patients with medulloblastoma, those with ependymomas present with evidence of leptomeningeal dissemination at the time of diagnosis in only 5% of cases.⁶ The diagnosis of leptomeningeal metastases is made by contrast magnetic resonance (MR) imaging and/or cytologic examination of the cerebrospinal fluid (CSF). The results of both must be negative for a child to be ruled without metastatic disease. In children with ependymoma and a ventriculoperitoneal (VP) shunt, CSF obtained by lumbar puncture is more sensitive in detecting leptomeningeal disease.¹²

Relatively little is known of the pathogenesis of ependymomas compared with other childhood brain tumors. Ependymomas are thought to arise from radial glial cell precursors.¹³ In childhood, 90% of ependymomas are located intracranially, one-third supratentorially, and two-thirds infratentorially (► Fig. 41.1).¹⁴ Sixty percent of supratentorial ependymomas are in or adjacent to the ventricles, whereas the other 40% arise away from ependymal surfaces (► Fig. 41.2).

Infratentorial (posterior fossa) ependymomas are thought to arise from three different sites in the fourth ventricle: the floor (60%), the lateral aspect (30%), and the roof (10%).^{15,16} Tumors that arise from the floor often extend out through the foramen of Magendie over the dorsal aspect of the spinal cord. Tumors arising more laterally may extend out of the foramen of Luschka to involve the contents of the cerebellopontine angle (CPA).

41.2 Outcome and Prognostic Factors

Many authors have examined prognostic factors in ependymoma. The most important prognostic factor is extent of resection. Other clinical variables thought to be prognostic include extent of disease at diagnosis (M status), tumor location, tumor grade, and patient age at diagnosis. There is no formally recognized staging system for ependymomas, although the importance of leptomeningeal dissemination is well known. Children are staged at the time of diagnosis or shortly after surgery with cranial and spinal MR imaging as well as examination of cerebrospinal fluid (CSF) cytology. Long-term survival is uncommon in children with M+ disease.

41.2.1 Extent of Resection

The single most important determinant of outcome in cases of pediatric ependymoma is the extent of surgical resection. The pediatric neurosurgeon must achieve a maximal safe resection. The 5-year survival rate in children who receive a GTR is 67 to 80%, and the 5-year PFS rate is 51 to 75%.^{4-7,9-11,17-25} In striking comparison, the 5-year survival rate of children who undergo subtotal resection is 22 to 47%, and 5-year PFS rate is 0 to 26%. Thus, many authors suggest that pediatric patients with ependymoma and residual tumor on postoperative imaging undergo a repeated resection.^{16,19,26,27}

Many neurosurgeons classify ependymoma resections as gross total resection (GTR), near-total resection (NTR), subtotal resection (STR), and biopsy. The extent of surgical resection should be confirmed by postoperative MR imaging with and without gadolinium within 72 hours of resection to avoid confusing postoperative artifacts. A GTR is defined as absence of tumor on postoperative MR imaging. If a thin carpet of tumor is left on the floor of the fourth ventricle (and is visualized with the operating microscope at the time of surgery), but there is no evidence of tumor on postoperative MR imaging, this still qualifies as a GTR at St. Jude Children's Research Hospital (Memphis, Tennessee). A resection is subtotal when gross residual tumor (more than a fourth ventricular layer) remains after surgery that was visible to the surgeon or evident on neuroimaging. Although NTR was once thought to be prognostically similar to GTR and has been arbitrarily defined as less than 1.5 cm³ on postoperative imaging (similar to the values quoted for medulloblastoma) and/or a 0.5-cm residual thickness of tumor bed enhancement, longer follow-up has shown that these patients actually stratify more closely to

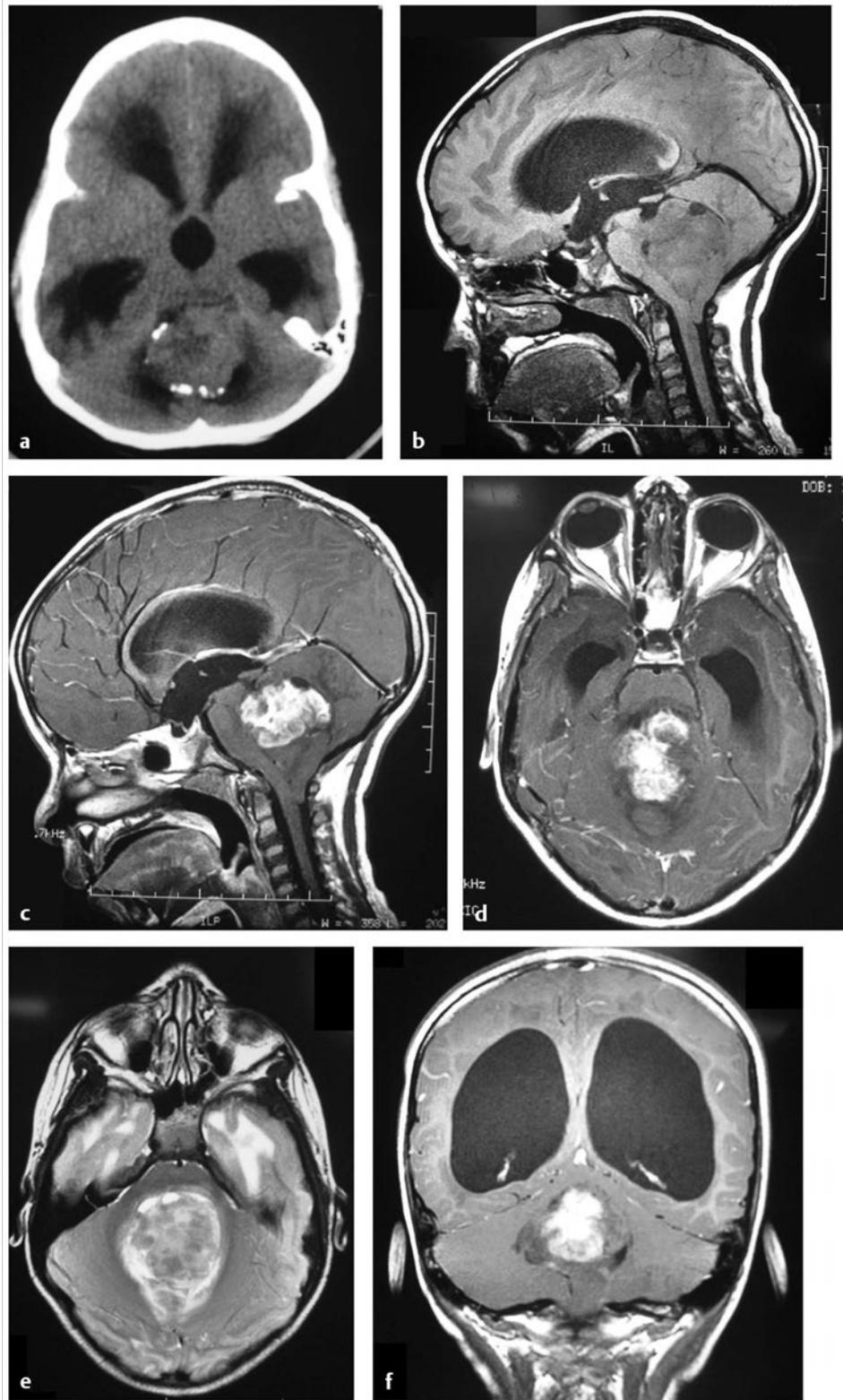


Fig. 41.1 A 5-year-old with headaches and vomiting. (a) An unenhanced computed tomography (CT) scan shows a posterior fossa tumor, with some peripheral calcifications. There is associated supratentorial noncommunicating hydrocephalus from obstruction of the fourth ventricle. (b) Sagittal T1-weighted magnetic resonance (MR) image without intravenous contrast shows a mass lesion in the fourth ventricle that is isointense or hypointense to the brain. Note that the tumor and the cerebellum have protruded down through the foramen magnum. (c) Sagittal T1-weighted MR image with intravenous contrast shows enhancement of the superior portion of the tumor. One of the critical pitfalls in ependymoma surgery is failure to recognize the nonenhancing portion of the tumor. (d) Axial T1-weighted MR image with contrast. (e) Axial T2-weighted MR image shows a high-signal mass lesion in the fourth ventricle. (f) Coronal T1-weighted MR image with contrast shows supratentorial hydrocephalus and the partially enhancing, partially nonenhancing tumor. The nonenhancing portion of the tumor is extending out through the foramen of Magendie.

patients with STR, making us even more aggressive about a return to surgery for small amounts of residual tumor; however, we do not return to surgery for a layer of tumor invading the floor of the fourth ventricle unless it is bulky disease.^{11,19} Recent studies, based upon molecular profiling of ependymomas, suggest that fourth ventricular ependymomas

that invade the floor of the fourth ventricle have a better prognosis than do lateral ependymomas, regardless of the extent of resection.² This is a very important concept for the pediatric neurosurgeon; it is not necessary to perform extensive, overly aggressive resections in this location (i.e., chase an ependymoma into the floor of the fourth ventricle)

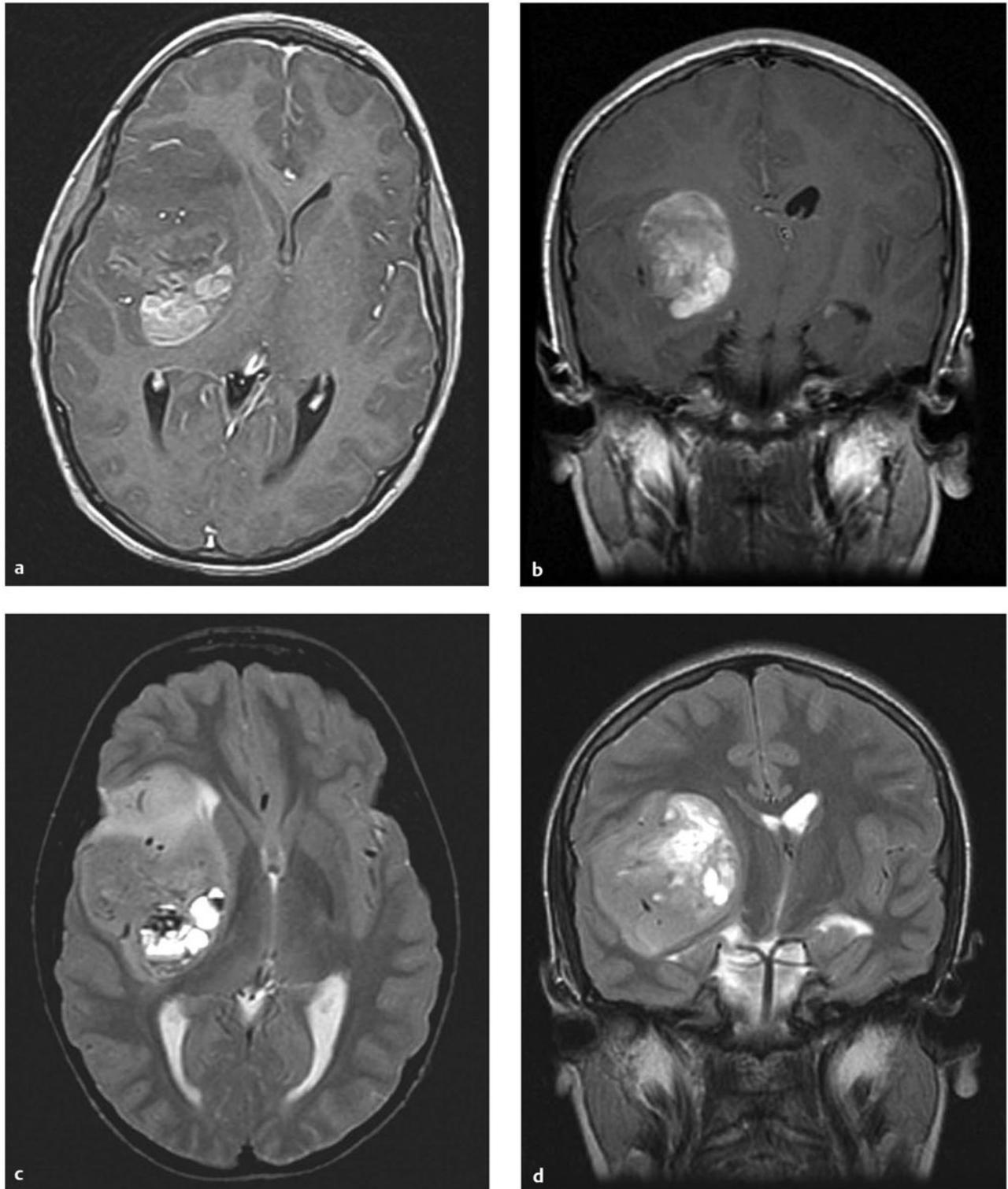


Fig. 41.2 Supratentorial ependymoma. (a) Axial T1-weighted magnetic resonance (MR) image with gadolinium shows a hemispheric mass lesion, partially enhancing, partially nonenhancing, in the right frontal operculum. (b) Coronal T1-weighted MR image with gadolinium. (c) Axial T2-weighted MR image. Note the paucity of peritumoral edema. (d) Coronal T2-weighted MR image.

because doing so will not increase the chance of cure enough to justify the risk for harm. The most valuable tool in the assessment of extent of resection is postoperative MR imaging because the surgeon's judgment is notoriously suspect.

41.2.2 Histologic Grading

There are numerous articles in the literature both supporting and refuting the value of histologic grading in determining the prognosis of patients with ependymoma.^{6,11,20,22,23,28-31} Anaplastic ependymoma exhibits histologic evidence of advanced anaplasia, including nuclear atypia, marked mitotic activity, a high level of cellularity, microvascular proliferation, and/or necrosis. Part of the reason for the controversy in the literature is the inability of pathologists to agree on what constitutes an anaplastic ependymoma. A study from the Children's Cancer Group (CCG) showed that 22 of 32 cases (69%) had a discrepancy in the diagnosis at the time of central pathologic review.¹¹ Ellison et al reported less than 50% agreement among five experienced neuropathologists across three multicenter studies of ependymoma. Four of five agreed only 70% of the time.³²

Analysis of a group of 50 contemporary patients with ependymoma from St. Jude Children's Research Hospital showed that tumor grade was significantly related to PFS after irradiation ($p < 0.001$).¹⁹ In this group of patients, 2-year event-free survival (EFS) was $32\% \pm 14\%$ for children with anaplastic ependymoma and $84\% \pm 7\%$ for children with classic ependymoma. This association remained significant after adjustment for ages less than 3 years, chemotherapy, and extent of resection. Supratentorial ependymomas were more likely than posterior fossa ependymomas to show anaplastic histology.

Recently, attempts at more simple risk stratification have been reported.³³ Gain of chromosome 1q and STR reliably placed patients into a high-risk category independently of histopathologic analysis. Cell density and mitotic count were used in the model to add specificity; however, mitotic count did stratify out an intermediate-risk category (► Fig. 41.3). It did not improve the prediction over 1q status and totality of resection alone.

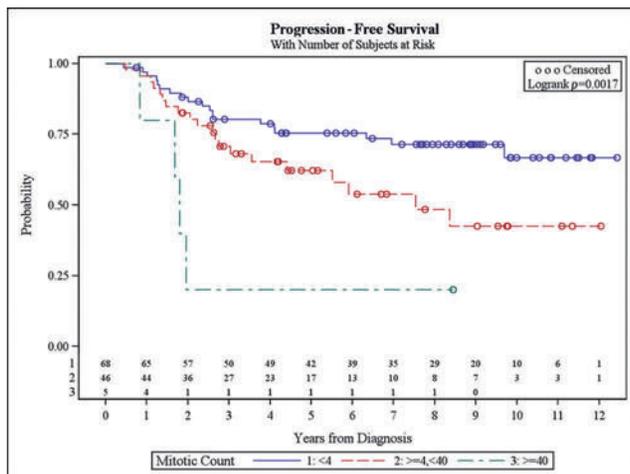


Fig. 41.3 Progression-free survival with number of subjects at risk. (Courtesy of David Ellison.)

41.2.3 Age at Diagnosis

Children less than 3 years of age at the time of ependymoma diagnosis have a poor prognosis when compared with older children. Several factors may account for this. Tumors in children of this age have a different molecular pathophysiology (see below) and may have more aggressive clinical behavior. Younger children are more fragile and have increased complications of surgery, radiation, and chemotherapy. Clinicians are reluctant to give radiotherapy to children less than 3 years old, or they give lower doses of radiation supplemented by chemotherapy. Pollock reported a 5-year survival rate of 22% and a PFS rate of 12% in children less than 3 years of age. Older children had 5-year survival rates of 75%, and the PFS rate was 60%.¹⁰ A study by the Pediatric Oncology Group (POG) showed a 63% 5-year survival rate for children 24 to 35 months of age (with radiation delayed 1 year by the use of chemotherapy), but only a 26% 5-year survival rate for younger children (0 to 23 months, radiation delayed 2 years).³⁴ The data of Merchant would suggest that the poorer prognosis in young children is more likely related to delayed or reduced-dose radiation. Historically, children who receive radiotherapy have had an increased survival compared with those who do not.^{35,36}

41.2.4 Pathology

Ependymomas are classified as glial tumors, and their diagnosis is often straightforward. Histologic grading is more difficult, and it is controversial, as discussed earlier. A pathologic diagnosis is made by histologic examination supplemented by immunohistochemistry. Ependymomas are moderately cellular neoplasms with monomorphic nuclei. Perivascular pseudorosettes and less commonly true ependymal rosettes can be seen on histology. Endothelial proliferation is seldom seen in classic ependymoma. The World Health Organization (WHO) classification defines grade II ependymoma as follows: mitoses rare or absent; occasional foci of palisading necrosis; nodules with increased cellularity, and mitotic activity.³⁷ Ependymomas usually stain positively for glial fibrillary acidic protein (GFAP).

Anaplastic ependymoma (AE) is a grade III lesion in the WHO classification.³⁷ Tumors with clear ependymal differentiation, perivascular pseudorosettes, increased cellularity, cytologic atypia, and microvascular atypia are diagnosed as AE. Areas of hypercellularity may be diffuse or focal and may form well-circumscribed regions. Additionally, areas of cytologic atypia, including an increased nuclear-to-cytoplasmic ratio and cellular pleomorphism, may be seen. Anaplastic regions often have a higher mitotic rate, although no specific threshold for a diagnosis of AE is in wide acceptance. The 2000 WHO criteria for AE include increased cellularity, brisk mitotic activity, vascular proliferation, and pseudopalising necrosis.³⁸ Neither focal areas of atypia nor brisk mitotic activity is sufficient to make a diagnosis of AE. It is unclear whether AE arises from progression or malignant degeneration of classic ependymoma or if it occurs de novo. Failure to find true ependymal rosettes or perivascular pseudorosettes is associated with a poor prognosis in children with ependymoma.¹⁷ Two separate groups have reported that the combination of necrosis, endothelial proliferation, and a mitotic index above 5 was a negative predictive factor for overall survival (OS) and PFS.^{17,39}

There is an inverse relationship between survival and mitotic rate demonstrated by proliferating cell nuclear antigen (PCNA), Ki-67, and MIB-1 labeling studies of ependymomas.^{17,25,39–41} However, one group found that mitotic rate was important only in determining the prognosis of supratentorial ependymomas.⁴²

Worse survival is related to increased expression of the following: p53, topoisomerase II- α , B-cell lymphoma-2 (Bcl-2), tenascin, vascular endothelial growth factor (VEGF), and epidermal growth factor receptor (EGFR).^{25,43,44} Nuclear expression of the apoptotic protein Survivin portends a good prognosis in breast and gastric cancer, and low levels of nuclear Survivin were seen with higher-grade ependymoma than with classic ependymoma.⁴⁵ Although these various molecular findings require further verification with prospective data, they may represent an additional opportunity to stratify ependymomas objectively, beyond the gain of chromosome 1q mentioned earlier, based on their biology.³³

There is mounting evidence that among the classic supra- and infratentorial and spinal ependymomas there are distinct cytogenetic differences that dictate their biology. These differences are likely based on differing progenitor cells or differentiation at different points during embryologic development. The group at St. Jude Children's Research Hospital has made significant advances in understanding the molecular basis of ependymomas. They used mRNA profiles to segregate ependymomas by central nervous system (CNS) location and unmasked previously unknown subgroups among supratentorial, posterior fossa, and spinal ependymomas, classifying ependymomas into nine distinct subgroups (subgroups A through I).¹ They identified potential ependymoma oncogenes, which included several regulators of stem cell proliferation, pluripotency, and neural differentiation. These include *THAP11*, *PSPH*, *EPHB2*, 10 genes within the *PCDH* cluster, *KCNN1*, *RAB3A*, *PTPRN2*, and *NOTCH1*. This finding allowed the researchers to create the first ependymoma mouse model. The specific combination of embryonic cerebral radial glial cells, deletion of *Ink4a/Arf*, and amplification of *EphB2* generated supratentorial ependymomas.¹

Researchers from Toronto and Heidelberg confirmed these findings in 2011 with a study that examined two independent cohorts of patients with posterior fossa ependymoma.² Using a combination of cytogenetic techniques, they grouped tumors into three distinct biological groups—a supratentorial ependymoma and two posterior fossa subtypes. The two posterior fossa subtypes were indistinguishable under the microscope. The groups were segregated into group A (younger, male, balanced genome, WHO grade III, CPA location, invasive, recurrent, metastatic, worse survival) and group B (older, gender-balanced, unbalanced genome, fourth ventricular location, rarely invasive, rarely recurrent, rarely metastatic, good survival). PFS and OS rates for group A were 44% and 65%, respectively. The corresponding rates in group B were 75% and 95%, indicating that although the tumors are histologically identical, they are distinctly different diseases. The investigators found group A tumors to be LAMA2+/NELL2- and group B tumors to be LAMA2-/NELL2+.

The ability to stratify ependymoma patients will allow clinicians to identify which of them will require more aggressive and/or novel therapies. Future clinical trials should include an

assessment of the status of these markers and their correlation with response to therapy, PFS, and OS.

41.3 Types of Ependymoma

There are several variants of ependymoma that have distinct histologic appearances or that exhibit unique biology. These ependymoma variants all show evidence of ependymal differentiation on electron microscopy; however, they likely represent entities that are distinct and separate from classic ependymoma. Thus, a collection of diseases exists that should be called the ependymomas.

41.3.1 Myxopapillary Ependymomas

This variant of ependymoma occurs in the filum terminale or conus (► Fig. 41.4) and in the adult literature is very indolent. In the pediatric literature, myxopapillary ependymomas are not so indolent; they are more likely to recur and to metastasize.^{46,47} Patients typically present with pain, lower extremity weakness, numbness, and bladder dysfunction.⁴⁸ The diagnosis is often delayed because of the nonspecific nature of the presentation.⁴⁹ Myxopapillary ependymoma appears on imaging as an extramedullary tumor, or as a tumor growing out of the conus (► Fig. 41.4). Compared with other spinal tumors, myxopapillary ependymomas can have a high signal on T1-weighted MR imaging, perhaps because of their high content of mucin.⁵⁰ Myxopapillary ependymomas in adults are cured with total excision. Less so in children. Subtotal resection followed by local radiation therapy is used to minimize neurologic deficits in cases in which the tumor is deemed unresectable.^{48,51,52} Uncommonly, myxopapillary ependymomas may metastasize, at which time they can be successfully treated with craniospinal irradiation, with the recognition that craniospinal irradiation in children is quite morbid.⁵³ As such, the authors feel strongly that incompletely resected myxopapillary ependymomas in children should not be observed but should be treated, either with return to surgery for GTR or with focal irradiation if unresectable. Histologically, the tumors appear as cuboidal cells arranged around a fibrovascular core with extensive areas of intrapapillary mucin. Myxopapillary ependymomas show a distinct biology; gains of chromosomal material on chromosomes 9 and 18 are seen in most tumors that are not commonly seen in classic ependymoma. It remains unclear what biological relationship (if any) myxopapillary ependymomas have to classic ependymomas.

41.3.2 Clear Cell Ependymomas

This ependymoma variant occurs preferentially in children and is usually found in the supratentorial compartment.⁵⁴ Histologically, it may be mistaken for other clear cell neoplasms, including oligodendroglioma, central neurocytoma, hemangioblastoma, and renal cell carcinoma.⁵⁴ Electron microscopy is invaluable in the diagnosis of this variant; it shows ependymal features, including microvilli, cilia, and junctional complexes.^{55,56} Cysts with enhancing walls were seen in 9 of 10 patients with clear cell ependymoma.⁵⁴ The

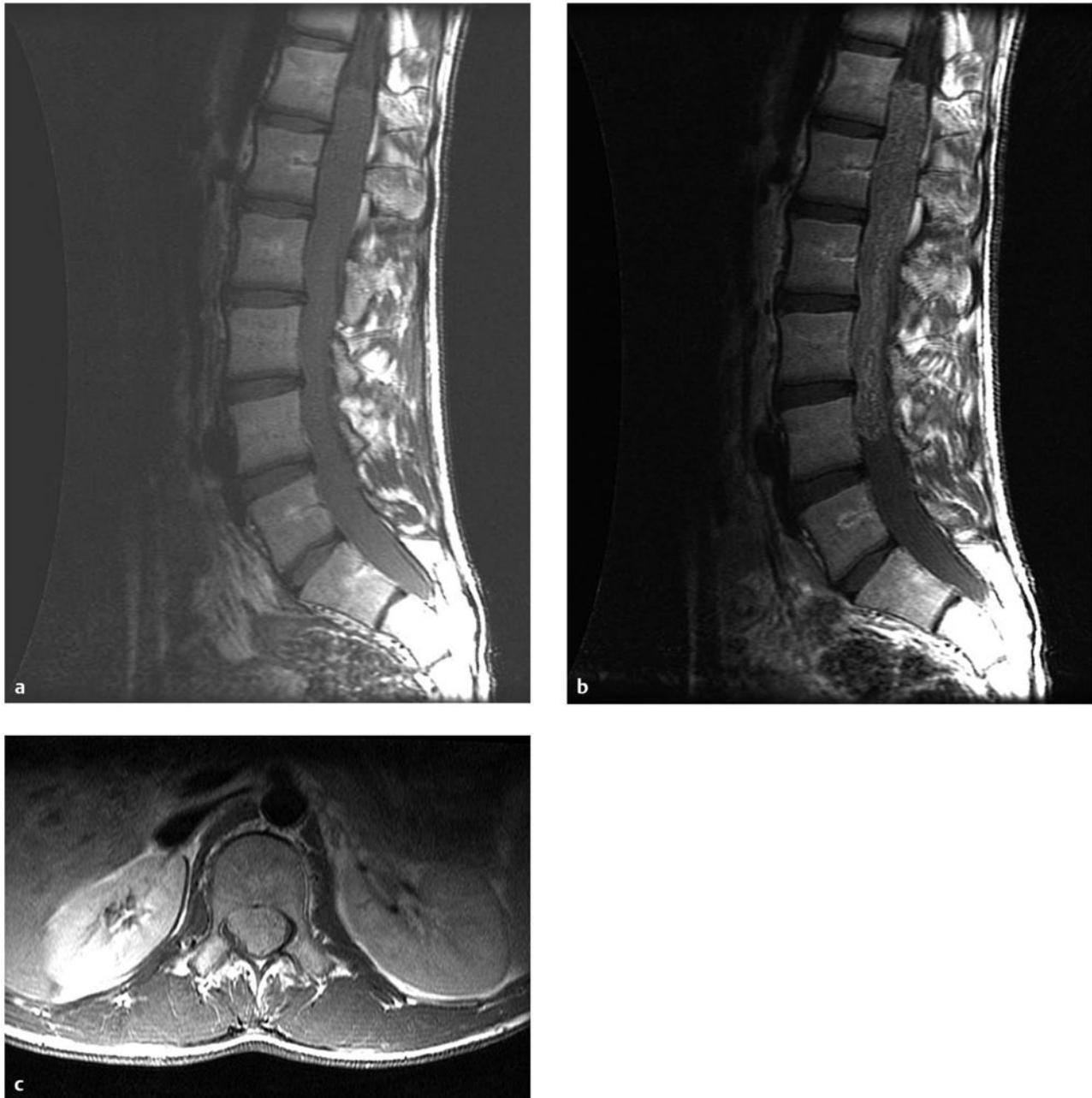


Fig. 41.4 Myxopapillary ependymoma in a child with back pain. (a) Sagittal T1-weighted magnetic resonance (MR) image without contrast shows an intradural tumor filling the thecal sac in the low thoracic and lumbar spine. (b) Added intravenous contrast better defines the tumor and shows that it extends from T12 to L4. (c) Axial image shows the tumor filling the thecal sac, displacing the nerve roots to the periphery of the sac.

PFS and OS rates at 5 years in a recent series of clear cell ependymomas were $34\% \pm 20\%$ and $75\% \pm 19\%$, worse than those for classic ependymoma.⁵⁴ In that series, 2 of 10 patients developed extra-CNS metastases.⁵⁴ Clear cell ependymomas showed frequent loss of genetic material on chromosome 18, a finding specific to the clear cell variant that is not commonly seen in classic ependymoma. These are probably biologically unrelated tumors.

41.3.3 Intramedullary Spinal Cord Ependymomas

Ependymomas within the spinal cord (► Fig. 41.5) typically present with myelopathy, back pain, weakness, bowel and/or bladder deficit, or scoliosis.⁵⁷ The presence of an intramedullary ependymoma of the spinal cord in a young child should prompt one to consider neurofibromatosis type 2 (NF-2).

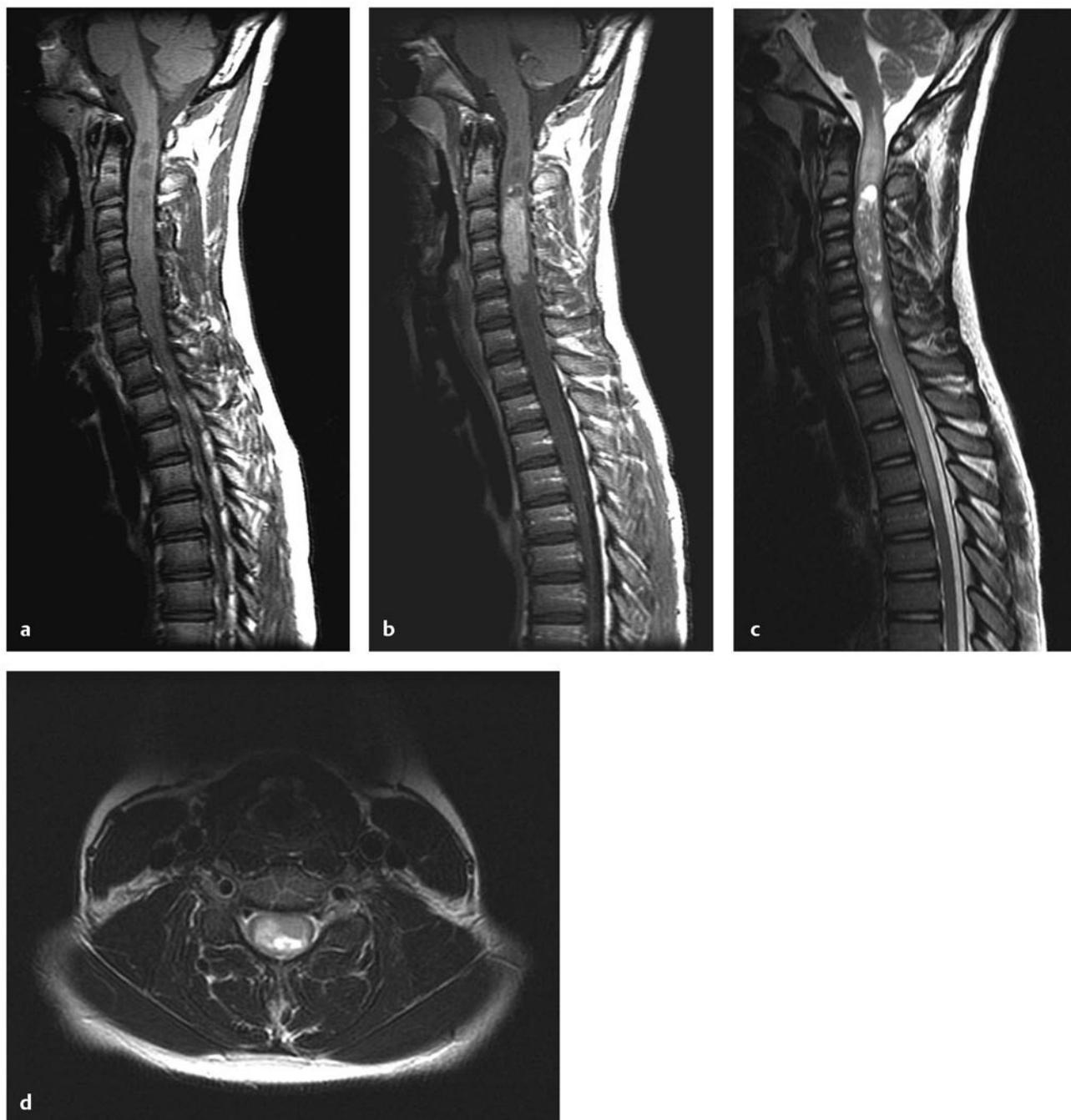


Fig. 41.5 (a) Cervical intramedullary ependymoma. (a) Sagittal T1-weighted magnetic resonance (MR) image without contrast shows areas of low signal within an expanded cervical spinal cord. (b) Sagittal T1-weighted MR image with contrast shows an enhancing mass lesion (ependymoma) within the cervical spinal cord. Cystic areas (syrinxes) are seen both superior and inferior to the mass lesion. (c) Sagittal T2-weighted MR image shows the intramedullary tumor and the adjacent syrinxes. Edema of the spinal cord is seen extending rostrally to the brain stem. (d) Axial T2-weighted MR image shows expansion of the cord with abnormal signal.

Intramedullary ependymomas are more discrete than intramedullary fibrillary astrocytomas and thus are easier to completely resect because of the presence of an obvious tumor–spinal cord interface. Current treatment for these rare tumors at St. Jude is maximal safe resection followed by focal radiotherapy.⁵⁸ Of only 4 patients with intramedullary ependymoma treated at St. Jude, 2 are dead of disease.⁵⁸ In a recent mixed

series of 67 adult and pediatric tumors, GTR was the stated preoperative goal, and when it was achieved (55 cases), no postoperative radiation was performed.⁵⁷ There were only 3 recurrences in the patients with initial GTR, and 2 underwent repeated operation for GTR. Radiation was reserved for patients in whom GTR was not achieved. Although intramedullary ependymomas are histologically similar to intracranial endy-

omas, they have a distinct biology. Patients with NF-2 are prone to developing spinal ependymomas. Moreover, sporadic intramedullary ependymomas, but not sporadic intracranial ependymomas, have somatic mutations of the *NF2* gene. This demonstrates that although intracranial and intraspinal ependymomas are histologically similar, they differ in biology and thus would be expected to have distinct natural histories and responses to therapy.

41.3.4 Tanycytic Ependymomas

Tanycytic ependymomas are an uncommon variant, with fibrillary cells that usually extend to the lumen of the ventricle.⁵⁹ They may occur within the brain or the spinal cord.^{59,60} True ependymal rosettes are absent, and perivascular pseudorosettes are sparse.⁵⁹ This ependymoma variant is often difficult to differentiate from an astrocytoma or a schwannoma. Immunohistochemistry is positive for GFAP and S-100.⁵⁹ This variant is thought to arise from tanocytes, a group of elongated unipolar and bipolar cells that extend between the ventricular lumen and the surface of the CNS. The ependymal nature of these tumors has been demonstrated based on their electron microscopy characteristics.⁵⁹ Although reports of tanycytic ependymoma are sparse, it should be recognized. It is likely an indolent variant, and aggressive therapies should be used with caution.^{59,60}

41.4 Genetics

Intramedullary spinal ependymoma is well known to occur in patients with NF-2; however, patients with NF-2 are not at increased risk for the development of intracranial ependymomas. Mutations of the *NF2* gene, located on chromosome 22q, are not found in intracranial ependymomas, myxopapillary ependymomas, or tanycytic ependymomas.^{61,62} Although intracranial ependymomas are well known to show loss of genetic material on 22q, they do not harbor *NF2* mutations, suggesting the existence of another, distinct ependymoma tumor suppressor gene in this region of the genome.

Classic ependymoma is reported in patients with the Li-Fraumeni familial cancer syndrome (*TP53* tumor suppressor gene).^{63,64} However, somatic mutations of *TP53* are not commonly found in sporadic ependymomas and likely do not play a large role in their pathogenesis.^{65,66} Scattered reports of patients with ependymoma and Turcot syndrome (brain tumors plus colonic neoplasia) are found in the literature, with some patients developing more than one ependymoma.⁶⁷⁻⁶⁹ These patients have germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5 and have overactivity of the Wnt signaling pathway. The role of the *APC* gene and/or Wnt signaling in sporadic ependymomas has not been elucidated. Spinal ependymomas have also been reported in the context of the multiple endocrine neoplasia type 1 syndrome due to mutation of a tumor suppressor gene on chromosome 11q13.^{70,71} Other families have an increased incidence of ependymomas, but no currently recognized familial tumor syndrome has been reported.⁷²⁻⁷⁴

41.4.1 Cytogenetics

As a group, ependymomas studied by G-banding karyotype show a frequent loss of genetic material on chromosomes 22q,

6q, 9q, 17p, and 11q and show a gain of genetic material on chromosome 1q.^{62,64,75-80} Loss of heterozygosity on chromosome 22q is more common in adult ependymomas and intramedullary spinal ependymomas and less common in pediatric ependymomas.⁶⁴ There is some evidence that the gain of genetic material on chromosome 1q may be an early event in the initiation of ependymoma.⁷⁵ A 1q gain stratifies patients into a higher-risk group.³³ Subsequently, several groups have published studies in which the technique of comparative genomic hybridization was used to study ependymomas.⁸¹⁻⁸⁷ This technique is more sensitive than a G-banding type karyotype at finding gains and losses of genetic material. Ependymomas from very young children frequently show a balanced karyotype (no observed gains or losses).⁸¹ Classic ependymomas from the brain and those from the spine have different cytogenetic profiles. Tumors with gain of chromosome 1q tend to occur in the posterior fossa in children, and the tumors often behave aggressively.⁸¹ Recurrent tumors show more extensive karyotypic abnormalities than the original tumors; whether this is due to biological progression or to random DNA damage from radiation and/or chemotherapy is not clear.⁸² Myxopapillary ependymomas show a higher number of cytogenetic abnormalities (average of nine per tumor) than do other ependymomas.⁸⁵ The most common changes seen in cases of classic ependymoma are gains of chromosomal material on chromosome arm 1q or chromosome 9 and losses of 6q, 22, and the X chromosome.⁸⁴

41.5 Imaging Studies

MR imaging is central to the diagnosis, management, and follow-up of children with ependymoma. Anatomical definition is required before surgery to determine the extent of tumor growth because some ependymomas have a propensity to grow out of the foramen of Luschka into the CPA or out of the foramen of Magendie into the cervical spine. MR imaging is also used to plan radiotherapy and to judge response to chemotherapy when it is given. Rarely, a child may present in extremis, and an operation will be done without preoperative MR imaging.

Most children with ependymoma should have pre- and postoperative imaging of the brain, and either pre- or postoperative imaging of the entire spine. Postoperative brain imaging should be done within 72 hours of surgery because after this time postsurgical artifact may make it difficult for radiologists to determine the extent of resection. If this 3-day window is missed, MR imaging should be delayed for a couple of weeks, at which time the artifact from surgery is decreased. Gelfoam (Pfizer, Cambridge, MA and La Jolla, CA) or Surgicel (Johnson & Johnson, New Brunswick, NJ), used for hemostasis at the time of surgery, can make the postoperative images difficult to interpret and may enhance over time, causing confusion with recurrent tumor. Leaving such material in the wound is therefore strongly discouraged.⁸⁸

Most ependymomas are variably enhancing. The T2 image helps determine the true extent of the tumor. Pre- and postoperative T1 films with and without gadolinium enhancement, as well as T2-weighted imaging, are necessary for comparison. Both the location and the extent of residual tumor are important in formulating a therapeutic plan.

The optimal frequency of surveillance imaging after treatment of ependymoma is uncertain. Most children with recurrence or progression present between 12 and 24 months after the initiation of radiation therapy. Early detection of recurrence should maximize the opportunity for salvage therapies. Some retrospective trials suggest that the early detection of asymptomatic recurrence of ependymoma leads to better outcomes than diagnosis when the recurrence becomes symptomatic.^{89,90}

Preoperative spinal imaging identifies patients (approximately 5%) who present with leptomeningeal dissemination. Subsequent surveillance imaging of the spine is problematic because there are many mimics of leptomeningeal disease, including blood products, infection, and inflammatory changes secondary to surgery or radiation therapy. Any spinal imaging that cannot be performed before surgery should be performed at least 7 to 10 days after any invasive CNS procedure. Leptomeningeal tumor usually appears as a series of small nodular tumors, or as thick disease coating the subarachnoid space focally. Diffuse “sugar coating,” such as that seen in medulloblastoma, is seldom seen in ependymoma, and leptomeningeal should not be diagnosed if there have been any recent invasive procedures on the CNS.

Complete responses to either radiation or chemotherapy are uncommon in children with ependymoma, although partial responses are often seen. After radiation, most ependymomas will diminish in size over a period of years and many show loss of contrast enhancement due to a loss of vascularity. Conversely, some ependymomas may show an increase in enhancement for the first several months after radiation because of an increase in leukocyte–endothelial interactions. This should not be misinterpreted as progression of the tumor. Recurrences in the first year after adequate radiation therapy are uncommon. Similarly, responses to chemotherapy manifest approximately 6 months after the start of treatment.

41.6 Surgical Treatment

Most children with ependymoma present with localized disease. Most recurrences are local. Subarachnoid dissemination is rare and fatal. This disease is well suited to therapies designed to achieve local control. The overriding value of GTR of ependymoma has been demonstrated in several institutional retrospective reviews and two prospective Phase III trials.^{4–7,9–11,20,23,34} Ependymoma is a surgeon’s tumor because this portion of the patient’s care has the highest impact on the quality and quantity of life.

Sutton et al retrospectively analyzed 45 patients with ependymoma and found that the 5-year survival for GTR or NTR was 60%, but with STR (defined here as <90% resection), it fell to 21%.⁷ Pollack et al found a 5-year survival rate of 80% after GTR, compared with 22% after less than GTR.¹⁰ Sutton et al retrospectively evaluated 92 children with ependymoma; the 10-year survival after GTR was 70%, and the PFS estimate was 57%.⁶ With STR, the 10-year survival was 32% and the 10-year PFS was 11%. Robertson et al prospectively treated 32 patients with CCG protocol 921 and found that the 5-year PFS rates were 66% for patients with less than 1.5 cm² of residual tumor and 11% for those with more tumor.¹¹ There is overwhelming evidence that cytoreductive surgery is beneficial to children with ependymoma and gives the best chance for long-term survival.

Two groups reported surgery without adjuvant treatments (i.e., radiation or chemotherapy) for children with ependymoma.^{21,88} Hukin et al described 10 pediatric patients who received only surgery as treatment for ependymoma; 8 tumors were supratentorial and 2 were in the posterior fossa.⁸⁸ At a median of 48 months of follow-up, 7 of the 10 patients were free of disease without having received adjuvant therapy. The other 3 patients had documented tumor recurrence at 9, 10, and 20 months after resection. Of the 3 patients, 2 were effectively treated with repeated surgery and radiation. Of the other 7 patients, another 2 went on to late failures. Little et al argued that deferring radiation in low-risk patients (older than 3 years, GTR, focal disease, lack of high-grade features) was a reasonable option.⁹¹ Palma et al reported success in treating supratentorial ependymomas with surgery alone.²¹ Surgery alone is probably a reasonable therapeutic option for children with supratentorial ependymoma with low-grade histology when the surgeon is able to take a rim of white matter around the tumor.

Although complete resection is of paramount importance in the treatment of ependymoma, it is achieved in only 42 to 70% of patients at initial resection.^{5,7,10,23,92} Complete resection is more readily achieved in supratentorial tumors and those that arise from the roof of the fourth ventricle. GTR of tumors that invade the floor of the fourth ventricle or pass out the foramen of Luschka to involve the lower cranial nerves is much more difficult, and surgical complication rates are higher.

41.6.1 Treatment of Residual or Recurrent Ependymoma

Most children who initially receive less than an NTR should have repeated surgery to reduce their status to minimal residual disease (GTR or NTR) (► Fig. 41.6). The exception to this may be those rare cases in which resection of the residual tumor will result in intolerable morbidity. In the case of surgery that is abandoned because of excessive bleeding, chemotherapy between resections may decrease the vascularity of the tumor, thus facilitating a safe return for repeated resection.⁹³ An evaluation of the initial approach may make obvious why the initial resection was STR. An alternate approach may make previously “hidden” tumor easy to resect. Second resections for ependymoma have an acceptable morbidity.²⁶ Although some complications were seen in 45% of children undergoing second-look surgery for pediatric CNS tumors, there was no significant change in mean functional scale scores at 4 or 24 weeks after surgery.⁹⁴ Foreman et al achieved GTR in four-fifths of a group of patients with ependymoma at the time of second surgery with no severe morbidity, and three of the patients remained progression-free at 23, 25, and 34 months after radiation therapy.²⁶

Recently, Massimino et al reported a progressive policy of second-look surgery in a multicenter trial. GTR rates for the entire group increased by 10 to 15% and by more than 50% in those undergoing second operations. They reported no additional major morbidity. The authors suggest that referral of these children with complicated cases to high-volume pediatric neurosurgery centers for their second-look surgery may improve outcomes.²⁷

In a series of 40 pediatric patients with ependymoma referred over a 3-year period at St. Jude Children’s Research

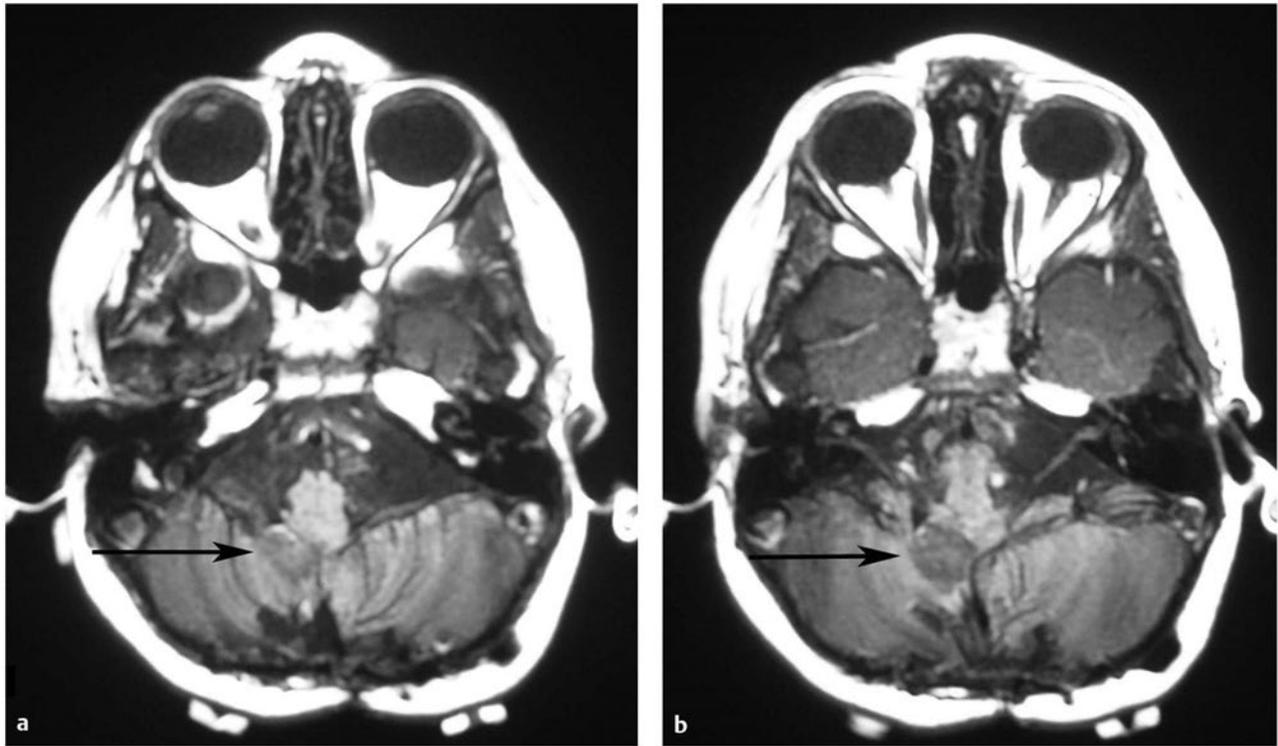


Fig. 41.6 Residual ependymoma after a first resection. (a,b) Postoperative magnetic resonance images after resection of a pediatric posterior fossa ependymoma show a small amount of nonenhancing residual tumor in the right foramen of Luschka. This residual tumor was resected at a repeated craniotomy, yielding a gross total resection.

Hospital, 24 of 40 patients (60%) had undergone complete resection, and 16 of 40 patients (40%) had residual tumor at the time of referral. Of those 16 patients with residual tumor, 12 were selected to receive additional surgery based on extent of disease, location of disease, and neurologic status at the time of referral. Of those 12 patients, a GTR was achieved in 10 and an NTR in the other 2 at the time of the second surgery; hence, the GTR–NTR resection rate for the entire cohort was 36 of 40 (90%). Successful GTR at the time of second-look surgery may prolong survival time as well as allow a lower dose of radiation to be used, thereby lowering the incidence of neurocognitive deficits.⁹⁴ Significant morbidity occurred in only one child at the time of second resection. Children who underwent repeated surgery within 30 days of the initial procedure had an improved performance level at 4 and 24 weeks after second surgery and a trend toward a lower complication rate compared with children who had second look surgery more than 30 days after the initial procedure.⁹⁴

Children with localized recurrent disease that is amenable to surgical resection should undergo repeated resection (► Fig. 41.7). If needed, referral to a high-volume pediatric neurosurgery center should be considered to maximize the chances of GTR without an increase in morbidity.

41.6.2 Surgical Technique

Careful preoperative scrutiny of the imaging is necessary to determine the extent of the tumor because ependymomas are notorious for extension through the foramen of Luschka out into

the CPA. Moreover, they often extend down through the foramen magnum into the upper cervical spinal canal. After adequate imaging interpretation, the goals of, and appropriate approach to, surgery will be decided. Interpreting ependymoma imaging can be difficult, given that there may be variable enhancement within the tumor. The T2 image and the FLAIR (fluid-attenuated inversion recovery) image often demarcate the extent of the tumor better than the T1 image. The preoperative imaging characteristics are important when postoperative imaging is interpreted, especially in the presence of residual or recurrent disease.

Childhood ependymomas can be functionally and molecularly divided into supratentorial, posterior fossa, and spinal tumors. The surgical management of supratentorial ependymomas is usually straightforward because the tumor is very distinct from the surrounding normal brain. Frameless stereotaxy localizes the scalp incision directly over the tumor. In areas of noneloquent brain, a thin rim of normal white matter should be resected around the ependymoma to ensure a complete resection. Ependymomas normally do not contain functioning neural tissue and can be resected safely from areas of eloquent cortex. Supratentorial ependymomas that are located entirely within the ventricles are rare. Many supratentorial ependymomas abut or compress the ventricle without entering the ventricle (► Fig. 41.2).

Preoperative surgical planning should classify a posterior fossa ependymoma as arising from one of the following:

- Cerebellar hemisphere
- Roof of the fourth ventricle

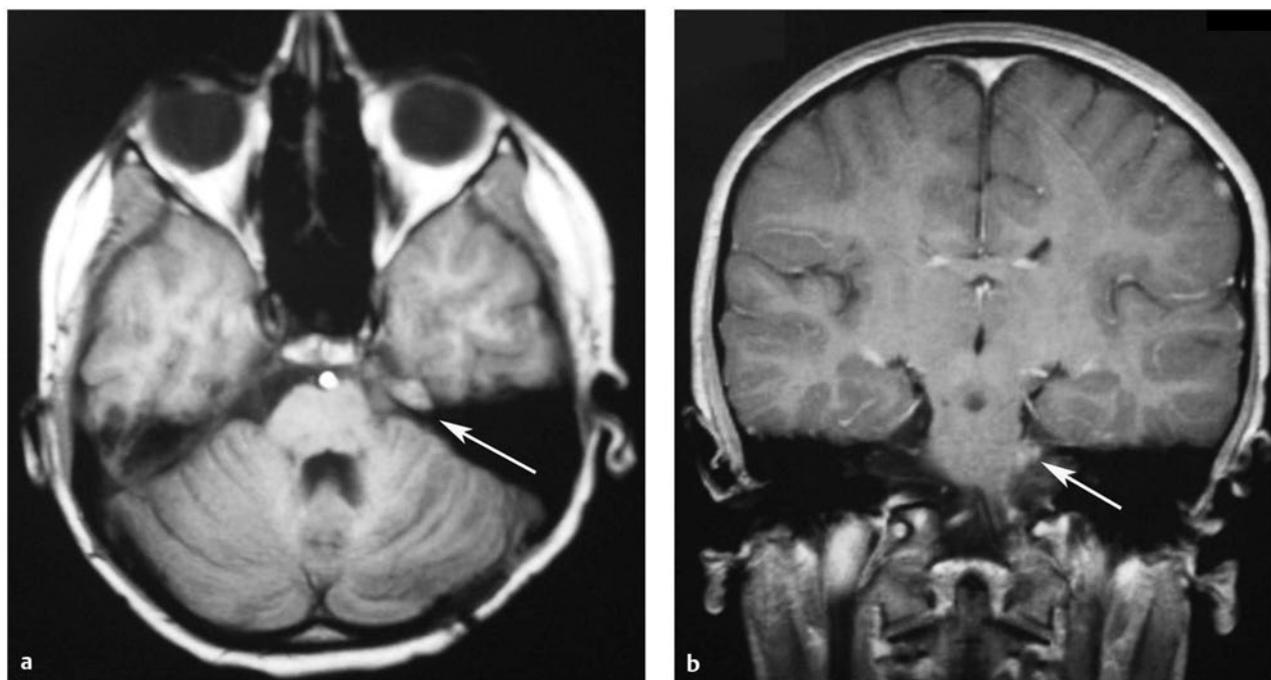


Fig. 41.7 Asymptomatic, recurrent ependymoma discovered on routine imaging. (a, b) This child with previous gross total resection and radiotherapy of a posterior fossa ependymoma was followed with routine magnetic resonance imaging. An asymptomatic recurrence was found in the left cerebellopontine angle, adjacent to the brainstem (*white arrows*). This was resected, and the child was treated with focal radiotherapy.

- Floor of the fourth ventricle
- Cerebellopontine angle (► Fig. 41.8)

Each location will dictate a different surgical strategy and entail a different set of surgical risks.

The patient is positioned prone with maximal tolerated flexion so that the floor of the fourth ventricle is sloping away from the surgeon. In the presence of hydrocephalus, a ventriculostomy may be placed before the posterior fossa is opened. The surgeon should release CSF slowly so as not to precipitate upward herniation or shifts in the tumor with consequent intratumoral hemorrhage. Craniotomy, as opposed to craniectomy, decreases the incidence of CSF leak and/or pseudomeningocele, and also diminishes the incidence of chronic postoperative pain.⁹⁵ The presence of a bone flap also facilitates surgery for residual and/or recurrent ependymoma. An appropriately sized craniotomy should be planned and executed based on the anatomy of the tumor. If needed, a C1 laminectomy is performed. The foramen magnum should be removed so as to increase exposure and to open pathways for CSF flow.

The dura is opened in a standard Y-shaped fashion. One should anticipate robust bleeding from an occipital and circular sinus and be prepared for management. If the dura over the cerebellum is tight, the dura over the upper cervical cord can be incised to allow the slow egress of CSF and relaxation. Alternatively, CSF can be withdrawn through a previously placed ventriculostomy. After the dura is opened, the cerebellar tonsils are separated to identify the posterior inferior cerebellar arteries. The vascular supply to a midline fourth ventricular tumor invariably comes off of the posterior inferior cerebellar artery

(PICA), distal to the tonsillar loop. Coagulation of large feeders to the tumor from the PICA devascularizes the tumor and results in a less bloody field.

Attention is next turned to the superior pole of the tumor, to define its margin circumferentially and then debulk it as it becomes devascularized. This continues until the aqueduct is visualized, opened, and covered with Gelfoam so as to prevent bleeding into the supratentorial ventricles, whereupon attention is turned to the inferior pole of the tumor. The inferior pole is dissected along its lateral and posterior margins, with care taken not to injure the floor of the fourth ventricle. At this point in the operation, it is often possible to determine if the tumor is arising from the roof or the floor of the fourth ventricle. If the tumor arises from the roof, complete excision is possible. The lateral margins of the tumor are dissected to diminish the tumor blood supply; then the tumor is debulked with either the bipolar suction technique or the ultrasonic aspirator.

Once the entire tumor has been removed, except for the portion invading the floor of the fourth ventricle, the surgeon should attempt to visualize the floor of the fourth ventricle both above and below the remaining tumor. The tumor should be resected down to the plane of the floor of the fourth ventricle. One should not chase bleeding below this line.⁹⁶ Judicious use of hemostatic products, mild tamponade, irrigation, and time will stop the bleeding. This technique usually results in minimal morbidity while leaving minimal residual tumor. Injury to this area through the overzealous use of bipolar cautery can cause permanent cranial nerve palsies as well as damage to the medial longitudinal fasciculus. At the end of the procedure, it is critical to look out the foramen of Luschka bilaterally to avoid missing a small piece of tumor.

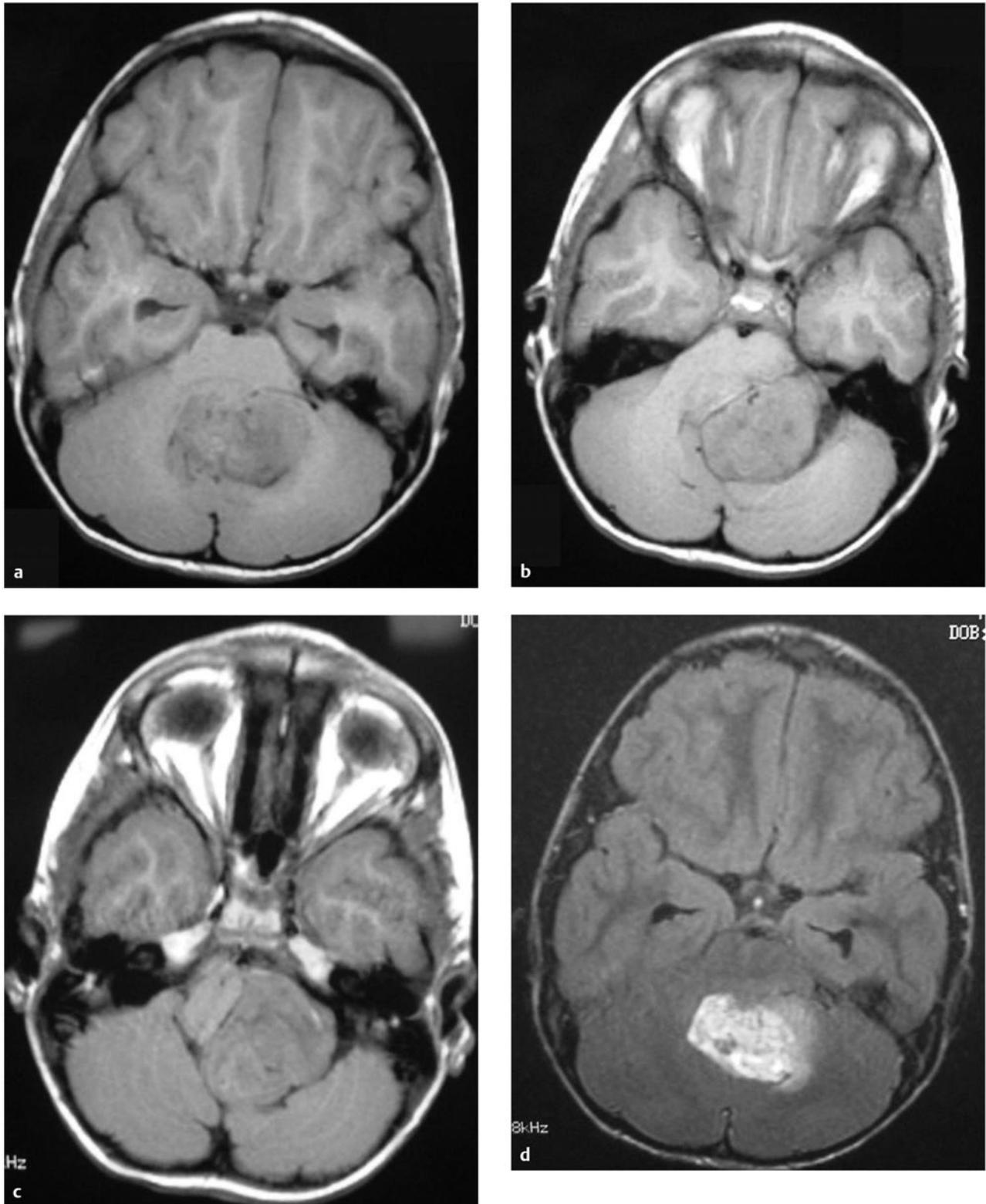


Fig. 41.8 A 7-year-old with 4 weeks of headache and vomiting. (a) An unenhanced T1-weighted magnetic resonance (MR) image shows a low-signal mass lesion within the fourth ventricle with extension into the cerebellopontine angle (CPA). (b) The extra-axial component of this tumor has severely compressed the brainstem and displaced it to the right. The anatomy of the displaced, rotated brainstem can be very confusing at the time of surgery. (c) Axial T1-weighted MR image with gadolinium shows enhancement of the lesion in the fourth ventricle. (d) The enhancing mass extends out of the foramen of Luschka. (*continued*)

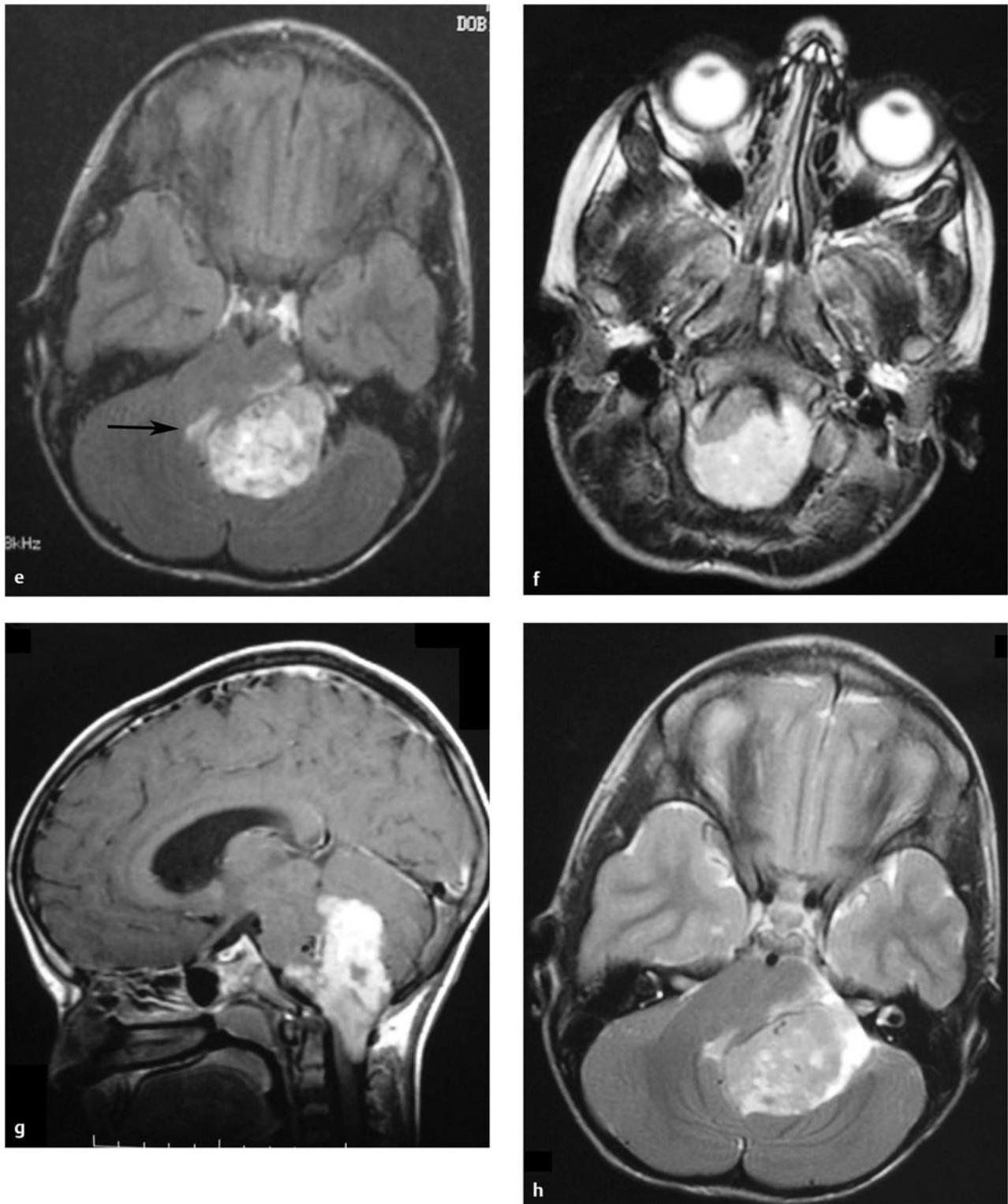


Fig. 41.8 (continued) (e) Partially enhancing, partially nonenhancing tumor around the lower brainstem. (f) Sagittal T1-weighted MR image with gadolinium shows enhancing tumor extending out into the CPA, as well as extending down into the cervical spinal canal. (g) Axial T2-weighted MR image shows a hyperintense lesion extending out of the foramen of Luschka on the left. (h) Axial T2-weighted MR image shows the mass effect on the brainstem, with the tumor, extending up to the basilar artery.

Care should also be taken to free the cerebellar tonsils and open the CSF flow pathways. Patch grafting of the dura may also help to open the CSF flow pathways and reduce the need for future shunt surgery. The bone flap is replaced.

CPA ependymomas originate from the lateral wall of the brainstem at the junction of the pons and the medulla (► Fig. 41.8). Their slow growth allows them to envelop multiple cranial nerves at the time of diagnosis (cranial nerves V through XII are at risk). Unilateral growth rotates the brainstem, distorting the normal anatomy and disorienting the surgeon. CPA ependymomas can grow through the foramen of Luschka into the fourth ventricle, filling it with tumor.

Like all posterior fossa ependymomas, CPA ependymomas have a blood supply from the PICA, with frequent contribution from the anterior inferior cerebellar artery (AICA), which runs through the CPA cistern. CPA ependymomas are often large by the time they come to clinical attention, and they predominantly occur in infants, making blood loss a major issue in their treatment. Transfusion should be planned for. High blood levels of potassium from the excessive transfusion of unwashed red blood cells in a very young child is unfortunately a cause of mortality.

Unlike many posterior fossa tumors, CPA ependymomas can often be diagnosed on preoperative imaging. Their removal is associated with very high rates of morbidity and mortality, even in experienced hands, and should be attempted only by surgeons who have experience with these tumors. Removal is accomplished by positioning the patient prone or in a park bench position with the head rotated so that the lateral portion of the cerebellum is highest. A far lateral craniotomy is performed. Knowledge of the vertebral artery anatomy is key in dissecting out laterally with the head rotated. The bone is opened along the sigmoid sinus, with removal proceeding as close to the jugular foramen as possible. If necessary, a C1 hemilaminectomy is performed. The dura is opened and the intraspinal portion of the tumor is removed first, with care taken not to injure the spinal roots. With the spinal portion removed, the vertebral artery and its PICA branch can be dissected free. The tumor is then debulked laterally until cranial nerves IX and X are identified entering the jugular foramen. Cranial nerves VII and VIII are identified in the CPA, and tumor is dissected away from them. A frequent cause of deafness after this operation is probably inadvertent sacrifice of the labyrinthine artery. This can be significant in children who may go on to receive ototoxic chemotherapy. After identification of the cranial nerves, the portion of the tumor within the fourth ventricle, which is generally not stuck in these cases, is removed before the lateral portion. This is accomplished by dividing the ipsilateral tela choroidea and inferior medullary velum such that the ipsilateral tonsil can be lifted up all the way to the foramen of Luschka. This allows a clear, unobstructed view of the entire fourth ventricle and ipsilateral foramen of Luschka. Once there is sufficient room in the posterior fossa, the most difficult part of the operation, removal of the tumor from the lower cranial nerves, is attempted. All feeding arteries originating from the major arteries and entering the tumor must be assumed to be brainstem perforating vessels until proven otherwise. These vessels must be preserved, or an unforgiving brainstem perforator stroke is possible.⁹⁶

Cranial nerve morbidity is high following removal of a CPA ependymoma. Children are maintained intubated until the vocal cords can be checked by an otolaryngologist. Vocal cord paralysis, when present, should be unilateral. Complete unilateral vocal cord paralysis in children who cannot handle their secretions mandates a tracheostomy. If there is some vocal cord movement, most children can be safely extubated and closely observed. Speech therapists should always perform swallowing studies on these patients.⁹⁷

It is not uncommon for a child to be able to manage his or her secretions (not require a tracheostomy) but still require a gastrostomy. Although many children have palsies of cranial nerves VI, VII, IX, and/or X postoperatively, more than 90% will recover within 3 to 6 months. Most children who initially require a tracheostomy or a gastrostomy will be able to have it removed during their convalescence.

One further complication of surgery for CPA ependymoma is that of residual tumor on postoperative imaging. In almost all cases, this should lead to a reoperation to achieve a GTR.

41.7 Treatment of Hydrocephalus in the Child with Ependymoma

Many children with ependymoma have hydrocephalus at the time of presentation, particularly those whose tumor is in the posterior fossa. Most neurosurgeons treat such children with corticosteroids until elective surgery can be performed. Preoperative shunting takes control of CSF drainage out of the surgeon's hands, with the recognized dangers of overdraining a child with a posterior fossa tumor (upward herniation and bleeding into the tumor due to brain shift). Those children who present in extremis may be treated with a ventriculostomy followed by definitive surgery to address both the tumor and the hydrocephalus.

Hydrocephalus is common in patients with posterior fossa ependymoma; however, it is much less common in patients with supratentorial ependymoma. Rarely, hydrocephalus may be seen in the setting of a spinal ependymoma as the consequence of high CSF protein levels secreted by the tumor. Hydrocephalus secondary to a posterior fossa tumor is due to occlusion of the fourth ventricle/aqueduct. In most children, removal of the fourth ventricular tumor, opening the aqueduct, and ensuring good flow of CSF at the level of the foramen magnum will restore CSF dynamics.

Postoperative hydrocephalus is rarely acute; more often, it develops slowly over a period of days or even weeks. The presentation is often the appearance of a pseudomeningocele or headache, nausea, vomiting, and lethargy. At times, postoperative hydrocephalus may be confused with posterior fossa syndrome. Asymptomatic, nonprogressive ventriculomegaly after fourth ventricular tumor excision should be observed over time rather than treated. In a child with symptomatic and/or progressive ventriculomegaly, treatment of the hydrocephalus is warranted. We favor an endoscopic third ventriculostomy as the initial hydrocephalus treatment unless the child has metastatic disease. If this is unsuccessful, a traditional shunt is placed. Both techniques have advantages and disadvantages that are beyond the scope of this chapter.

41.8 Adjuvant Therapy

41.8.1 Radiation Therapy

Postoperative radiation has been part of the standard therapy for patients with ependymoma since Mork and Loken showed that survival was 17% for patients who underwent resection alone, compared with 40% for those who underwent resection and radiation.³⁵ It may be acceptable to withhold radiation therapy in children with supratentorial ependymoma in whom a GTR has been achieved and in whom the pathology is classic WHO grade II ependymoma.^{35,72} There is little evidence to support radiation after GTR of an intramedullary spinal cord ependymoma.

A great deal of literature has focused on the dangers of radiation therapy in patients less than 3 years old with ependymoma. Numerous strategies to avoid or delay radiation have been proposed in this patient cohort in an attempt to minimize neurologic, endocrinologic, and cognitive morbidity. Although the side effects of administering radiation to very young patients with ependymoma have not been well documented, they are assumed to resemble those seen in infants with medulloblastoma, which are known. The POG-8633 study showed that young children with completely resected ependymoma in whom radiation was delayed for 2 years had a worse outcome (5-year survival, 38%) than did those children in whom radiation was delayed only 1 year (5-year survival, 88%).³⁴ Massimino et al reported the results of the AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) study, in which radiation therapy was deferred until age 3.⁹⁸ They found that survival was poor (overall survival rates of 48%, 37%, and 28% at 3, 5, and 8 years, respectively). They found no difference between the intellectual outcome of children receiving radiation at an age younger than 3 years and that of children with deferred radiation. These results suggest that delaying radiation in the treatment of focal ependymoma of infancy is not advisable.

Fewer than 5% of children with ependymoma have disseminated (leptomeningeal) disease at the time of diagnosis. Risk factors for dissemination include younger age, less than a GTR, a high proliferative index, and high-grade histology.⁹⁹ In most children with ependymoma who relapse, the relapse occurs at the primary site regardless of location or grade of the tumor.^{4,6,7} Multiple retrospective trials have failed to show the benefit of prophylactic craniospinal irradiation in the treatment of localized ependymoma.^{5,16,100,101} In light of these facts, the current recommendation at St. Jude Children's Research Hospital for nondisseminated ependymoma is localized radiotherapy. Craniospinal radiotherapy is reserved for children with leptomeningeal dissemination.

The radiation dose response level for ependymoma ranges from 45 to 60 Gy (gray), but the optimum dose of radiation remains unclear.¹⁹ Children with an STR (cannot benefit from further surgery) may benefit from dose escalation and/or hyperfractionation. Conformal radiation therapy (CRT) limits the highest dose of radiation to the primary tumor site (as opposed to administering radiation to the entire posterior fossa, for example) and decreases the dose received by normal tissues (especially the inferior portion of the temporal lobes). The role of CRT in the treatment of children with ependymoma was tested in a Phase II trial from 1997 to 2003 at St. Jude Children's

Research Hospital.¹⁹ Patients with localized ependymoma were evaluated before and after CRT to determine its neurologic, endocrine, and cognitive effects. Eighty-eight children (median age, 2.8 years) received irradiation therapy: 59.4 Gy in 73 patients and 54.0 Gy (age younger than 18 months and GTR) in 15 patients. GTR had been achieved through one or more craniotomies in 74 patients before irradiation, NTR in 6 patients, and STR in 8 patients. This study showed excellent results at 38.2 months, with 3-year actuarial EFS estimates of 74.7%. These impressive results show the value of GTR of ependymoma, and that effective targeting of ependymoma can be achieved by using conformal techniques without an increase in the relapse rate at the margin of the treatment volume. Children treated with CRT had their IQs evaluated before and after radiation, and surprisingly, their IQs were normal and did not significantly change during the study period (there was a trend toward improvement). The same group also published two reports finding that postoperative deficits were not made worse during CRT or improved during CRT.^{102,103} These results suggest that CRT is the preferred modality for radiotherapy in children with localized ependymoma and should not be delayed to allow recovery of postoperative deficits.¹⁹

Repeated irradiation is described by the St. Jude and Toronto groups.^{104,105} The St. Jude group treated 38 patients who had recurrent disease with repeated irradiation. In the St. Jude experience, radiosurgery had poor results, with 4 of 5 children dead of disease within a year of treatment, whereas craniospinal radiation resulted in a 4-year EFS rate of 53%. The Toronto group treated 18 patients who had recurrent ependymoma with repeated irradiation. They found an increase in 3-year OS (from 7 to 81%) and a longer time to progression. They documented 2 of 18 patients who had new endocrine deficits and noticed cognitive decline in the patients.

Radiosurgery has been used to treat several children with ependymoma, with good local control and no excessive neurotoxicity.^{8,106-108} When stereotactic radiosurgery should be used instead of open resection is not clear, but it is probably appropriate in children for whom anesthesia carries a high risk and in children with very small tumors that are in locations with high surgical risks. Currently at St. Jude, children who present with recurrent ependymoma within a previously irradiated field undergo maximal safe surgical resection of the recurrence followed by CRT to the tumor bed. Stereotactic radiosurgery has not proved beneficial in this group of children in our experience.

41.8.2 Chemotherapy

The role of chemotherapy in the treatment of childhood ependymoma is unclear; it does not make up part of the standard care of children with ependymoma. The response rate of ependymoma to single agents is 11%, with fewer than 5% showing complete responses.¹⁰⁹ Of the single-agent chemotherapeutics tried in ependymoma, cisplatin seems to be the most active.¹⁰⁹ In those rare children with ependymoma that responds to chemotherapy, there is no clear increase in survival. Several retrospective reviews have failed to show a benefit for cytotoxic chemotherapy in the treatment of newly diagnosed ependymoma.^{4-7,10,100,110} The CCG-942 randomized controlled trial compared children with ependymoma who received irradiation alone with those who received radiation and chemotherapy;

there was no survival benefit in the arm that received chemotherapy.³ Similarly, the POG-9233 trial did not show an overall survival benefit for infants with ependymoma treated with dose-intensive chemotherapy. The International Society of Paediatric Oncology (SIOP) trial treated 73 children with chemotherapy for 16 to 18 months after maximal resection; the children did not receive radiotherapy. PFS estimates at 2 and 4 years were 33% and 22%, respectively.¹¹¹ These results are clearly worse than those in historical controls treated with radiotherapy. One additional option being investigated is the superselective intra-arterial delivery of chemotherapy via the feeding arteries of recurrent/residual tumor.¹¹² Despite the best efforts of the neuro-oncology community, there is no clear role for current chemotherapy in the upfront treatment of children with localized ependymoma.

Chemotherapy may have a role in the treatment of children with residual tumor after an initial tumor resection. It has been suggested that the administration of chemotherapy between first and second craniotomies made the tumor borders more defined and easier to dissect.²⁶ Chemotherapy may also have a role in the treatment of children who need to delay surgery or radiation treatment because of illness or neurologic complications of the disease or its treatment. There is also benefit when chemotherapy is administered to very young infants with bloody tumors to reduce vascularity.⁹³

One reason that ependymomas have such a poor response rate to chemotherapy may be their expression of the *MDR1* gene, which is known to mediate drug resistance.^{113,114} Future research should include an examination of the effects of chemotherapy while the product of the *MDR1* gene is blocked.¹⁰⁹ Although GTR and CRT are the best treatments currently available for ependymoma, they are unlikely to improve drastically in the future. The development of novel chemotherapeutic strategies, particularly rational therapies based on the biological abnormalities found in the tumor, remains the best hope for future treatments.

Pearls

- Ependymoma is a neurosurgical disease, with local control the most important prognostic factor.
- Failure to obtain a GTR on postoperative imaging should usually prompt consideration of a second resection to improve the likelihood of long-term disease control, because achieving a GTR, compared with anything less, doubles the chances that a child will survive the cancer.
- CRT should be given to all children with localized ependymoma, except for a small minority with classic supratentorial tumors who undergo GTR.
- Although current cytotoxic chemotherapy has a little-proven role in the treatment of ependymoma, future therapeutics based on the biology of the disease offer hope for more effective, less toxic treatments.

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42 Brainstem Gliomas

Heather J. McCrea and Mark M. Souweidane

Brainstem tumors exhibit substantial heterogeneity in their clinical attributes, imaging features, anatomical position, and histologic subtype and grade. Accordingly, the clinical behavior of these tumors can be equally variable but is relatively well defined based largely upon the anatomical growth pattern, a feature that parallels magnetic resonance (MR) imaging findings. It is therefore important to categorize a patient's tumor based on this information in order to provide appropriate diagnostic and therapeutic recommendations.

42.1 Epidemiology

Brainstem tumors account for 10 to 20% of all central nervous system tumors in children.¹⁻⁴ Of brainstem gliomas, approximately 80% are diffuse intrinsic pontine gliomas (DIPGs), which carry a very poor prognosis.¹ However, roughly 15 to 20% are low-grade astrocytomas, and these follow a more indolent course. Approximately 150 to 400 children in the United States and 20 to 30 in the United Kingdom are thought to develop brainstem gliomas annually.^{1,3-7} The total incidence of brainstem tumors of all types rose from 0.31 per 100,000 between 1977 and 1981 to 0.67 per 100,000 between 1990 and 1994.⁵ This increase is primarily thought to be secondary to increased detection through the introduction of MR imaging rather than a true increase in the incidence of these tumors. There appears to be equal incidence regardless of gender. The most common age at diagnosis is 5 to 9 years, but cases have been seen in all age groups from infants to adults.⁶

42.2 Classification and Treatment Approaches

The classification of brainstem tumors is typically based on MR imaging.⁸ The overwhelming number of intrinsic brainstem tumors are astrocytic. Peculiarly, the histologic subtype and grade are fairly well predicted based on anatomical position or classification of the tumor. Tumors can be divided according to their location in the midbrain, pons, or medulla,⁸ and Epstein and Farmer suggested dividing tumors into three groups: cervicomedullary, focal medullary, and dorsal exophytic or diffuse anaplastic astrocytomas.⁹ Today, the classification of these tumors encompasses five principal and distinct subgroups: tectal (mesencephalic) tumors, DIPGs, focal tumors, dorsal exophytic tumors, and cervicomedullary tumors. Of course, not every brainstem tumor can be categorized as one of these defined entities, and the pathology may digress from the descriptive term. Because the current categorization scheme is defined by the anatomical features based on imaging, predicting the rare primitive neuroectodermal tumor (PNET) or ganglioglioma can be problematic, if not impossible. Therefore, any clinical or imaging aspects that raise suspicion about the conformity of the diagnosis should serve as an impetus for diagnostic sampling.

42.2.1 Tectal (Mesencephalic) Tumors

Approximately 5% of brainstem tumors are located in the tectal plate.¹⁰ They are most commonly indolent, slow-growing lesions limited to the rostral mesencephalon. Rarely, extension of the tumor into the posterior diencephalon occurs. They create symptoms primarily through the obstruction of cerebrospinal fluid (CSF) flow at the level of the cerebral aqueduct, resulting in symptomatic hydrocephalus.

On imaging, the tectal glioma is characterized by a thickened collicular plate with compression of the cerebral aqueduct. Resulting triventricular hydrocephalus is universally present unless the diagnosis is incidental. Because contrast enhancement is not likely, the mass is most easily seen on FLAIR (fluid-attenuated inversion recovery) and T2-weighted sequences on magnetic resonance (MR) imaging. The typical appearance includes hyperintensity on T2-weighted imaging and hypo- or isointensity on T1-weighted imaging (► Fig. 42.1).¹⁰ Lesions usually have poorly defined margins, although examples of focality have been reported.¹¹ Exophytic growth patterns are infrequent, but infiltrative growth into one or both thalami can occur with some regularity. This lack of exophytic growth into the quadrigeminal cistern helps to distinguish most mesencephalic tumors from tumors originating from the pineal gland. However, for large midbrain tumors and those extending into the pineal region, serum alpha fetoprotein, β -human chorionic gonadotropin, and placental alkaline phosphatase should be measured in order to rule out primary CNS germ cell tumors (discussed in Chapter 39, "Pineal Region Tumors").² The pathology of midbrain tumors, if obtained, is typically low-grade astrocytoma or more rarely ganglioglioma.^{10,12}

Surgical Treatment

The surgical treatment of midbrain tumors is typically restricted to the treatment of hydrocephalus. Given the obstruction to CSF flow at the level of the cerebral aqueduct, the currently preferred method for CSF diversion in these patients is an endoscopic third ventriculostomy (ETV). Patients occasionally require a repeat ETV, but overall, the literature suggests that 80 to 100% of patients undergoing ETV in this scenario remain shunt-free with excellent control of the hydrocephalus.¹³⁻¹⁵ With respect to the tectal tumor, surveillance monitoring with serial MR imaging is generally used, with more frequent imaging (3 to 6 months) shortly after diagnosis and then annually if the mass remains stable.^{2,16} Biopsy of these tumors is reserved for patients who exhibit a rapid neurologic course, unusual imaging features, or progressive radiographic findings. It is not recommended that a routine simultaneous endoscopic tumor biopsy be performed at the time of ETV for patients with typical clinical and imaging findings. For those with tumors that ultimately progress, tissue sampling is recommended. Suitable surgical approaches are determined based upon the degree of ventricular enlargement, tumor growth pattern, and focality of the mass.

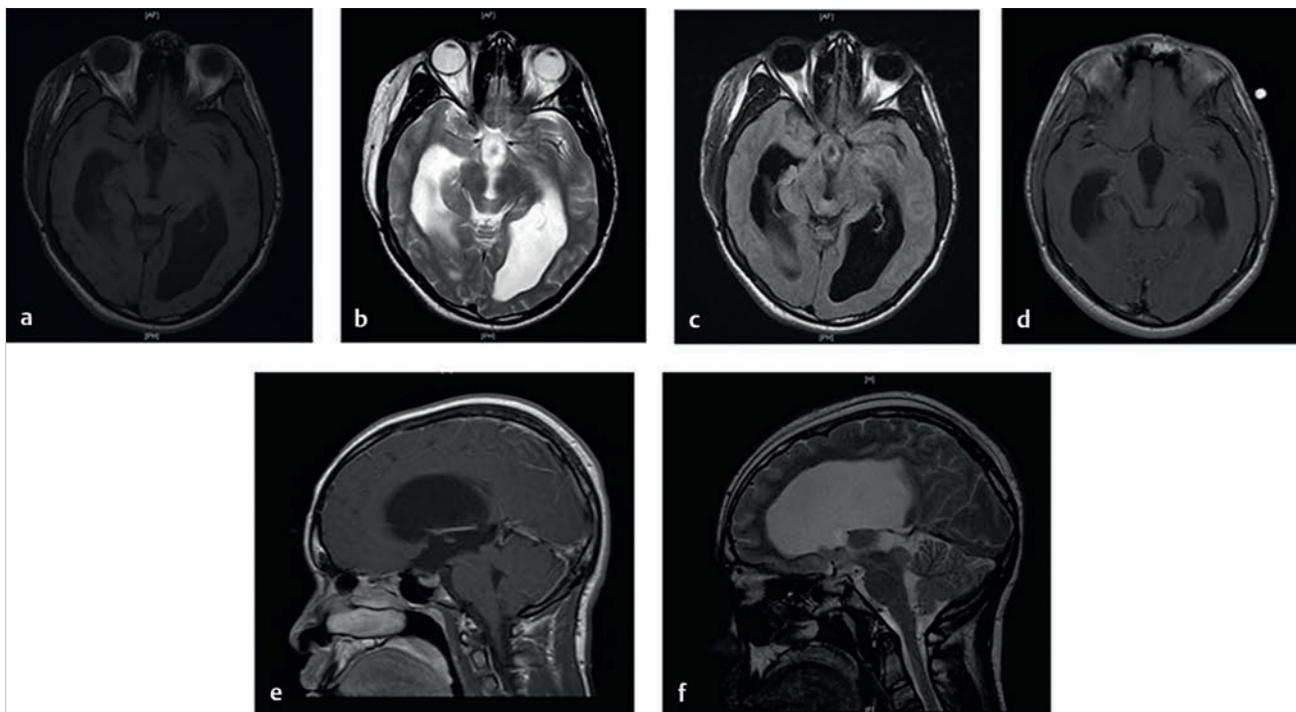


Fig. 42.1 Tectal mass. (a) Axial T1-weighted magnetic resonance (MR) image of a child with a tectal mass. Note significant resulting hydrocephalus. (b) Axial T2-weighted MR image and (c) axial FLAIR (fluid-attenuated inversion recovery) MR image for the same patient demonstrating hyperintensity. (d) Axial T1-weighted MR image with gadolinium contrast demonstrating typical lack of contrast enhancement. (e) Sagittal T1-weighted MR image with gadolinium contrast and (f) sagittal T2-weighted MR image.

Nonoperative Management

Patients with midbrain tumors typically do well, and conservative management after the treatment of hydrocephalus is often the most appropriate course. However, approximately 18 to 31% of tumors will eventually require treatment.^{10,17} The size at presentation appears to have a significant correlation with the need for future treatment. A recent study showed that all tumors larger than 10 cm³ at presentation ultimately required treatment, whereas the majority of those smaller than 4 cm³ did not require intervention.¹⁰ However, some patients with tumors in the smallest size subgroup do ultimately require treatment (13.6% in this series), so surveillance is recommended even in these cases of seemingly benign lesions.¹⁰ For patients whose tumors progress, one of a variety of approaches may be employed, such as irradiation, chemotherapy, or subtotal resection with irradiation of residual tumor. Both irradiation and surgery appear to be extremely effective; Pollack et al reported regression or stabilization in patients treated with irradiation, and Ternier et al reported control with surgery and repeated surgery if needed.^{10,17} Ternier et al reported only one death in their cohort of 40 patients.¹⁰

42.2.2 Diffuse Intrinsic Pontine Glioma

DIPG arises from the pons, is infiltrative, and may extend into the midbrain or cerebellar peduncles.¹⁸ Patients who have DIPG typically present with focal neurologic deficits and develop hydrocephalus only as a later sequela. Cranial nerve abnormalities most commonly manifesting as ocular imbalance are commonly

the first sign of these tumors. Other common cranial neuropathies include eye movement abnormalities, diplopia, dysphagia, dysarthria, and facial weakness or sensory loss.² Head tilting to compensate for diplopia may be noticed in children who are too young to describe visual problems. Cerebellar dysfunction is another common presenting sign of these tumors, and limb weakness can result from involvement of corticospinal tracts.^{2,19}

The MR imaging findings of DIPG are consistent with a hypocellular tumor that has more limited blood flow and angiogenesis than high-grade tumors. DIPGs are typically hypointense on T1 imaging and hyperintense on T2 and FLAIR imaging, with indistinct borders (► Fig. 42.2). Enhancement typically makes up only 0 to 25% of the tumor volume.¹⁸ Additional findings may include engulfment of the basilar artery or necrosis, but cysts are uncommon. MR spectroscopy shows a small decrease in *N*-acetylaspartate and an increase in choline, and MR perfusion demonstrates hypoperfusion.¹⁸ Atypical features include prominent enhancement, decreased T2 or FLAIR signal, restricted diffusion, and/or extensive exophytic components.

Although MR imaging is the standard modality for imaging brainstem lesions, advanced imaging modalities are under investigation and may prove useful in the future. A recent study of proton magnetic resonance spectroscopy in children with DIPG suggested that patients with an increased choline to *N*-acetylaspartate (Cho:NAA) ratio (thought to be suggestive of increased cell turnover, cell number, and neuronal damage) have a worse prognosis, and that an increase in this ratio from one time point to another is inversely associated with survival.⁶ This is consistent with studies in adult gliomas, which have shown that an increased Cho:NAA ratio correlates with a higher

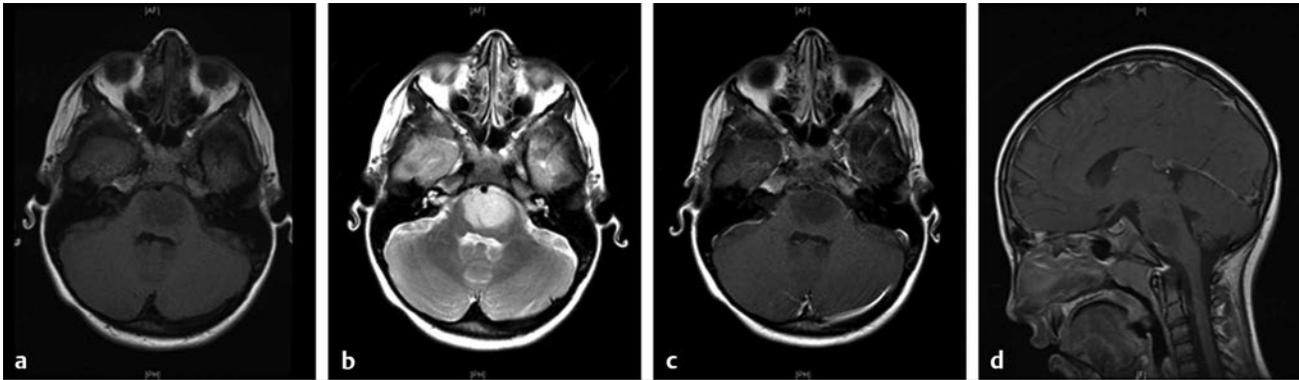


Fig. 42.2 Diffuse intrinsic pontine glioma (DIPG). (a) Axial T1-weighted magnetic resonance (MR) image of a child with DIPG demonstrating classic hypointensity and indistinct margin. (b) Axial T2-weighted MR image of the same patient demonstrating classic hyperintensity. (c) Axial T1-weighted MR image with gadolinium contrast demonstrating lack of enhancement. (d) Sagittal T1-weighted MR image with gadolinium contrast.

histologic grade.⁶ Positron emission tomography (PET) may also be of use in the assessment of DIPG, with two recent studies suggesting a trend toward a shorter length of survival in patients with increased fluorodeoxyglucose (FDG) uptake on PET.^{20,21} PET may also help in guiding stereotactic biopsy sampling because samples taken from areas with FDG uptake showed an equal or higher grade than areas without uptake, and in this small series the diagnostic yield was increased when PET information was used to guide the trajectory.²⁰

MR imaging appears to be very accurate for classifying tumor type in cases with classic findings. In a recent study correlating imaging findings with histology in 44 patients with brainstem tumors, 100% of diffuse nonenhancing brainstem lesions (i.e., cases with imaging features typical of DIPG) were found to be consistent with astrocytoma with predominantly low-grade features (8 low-grade cases and 1 high-grade case). Of the enhancing diffuse lesions (atypical of DIPG), 90% were diffuse brainstem glioma, with a much higher proportion of high-grade samples in these biopsies (14 high-grade and 4 low-grade cases). The tumors of the two patients in whom other pathologies were identified included 1 ependymoma and 1 ganglioglioma.²²

Surgical Treatment

Diffuse tumors are not resectable, and the role of biopsy in DIPG remains limited to tissue sampling for molecular therapeutic strategies or investigational purposes. Before the routine use of MR imaging, biopsies were performed to confirm diagnosis and provide information regarding prognosis. Since the advent of MR imaging, DIPG can often be diagnosed without biopsy. Albright et al argued that biopsies were frequently not indicated in children with brainstem lesions because the lesions could be diagnosed and treated solely on the basis of MR imaging without subjecting the children to the risk of biopsy.²³ An important aspect of diagnosis today involves differentiating between “classic” DIPG and “atypical” DIPG; “classic” DIPG is typically diagnosed solely on imaging, whereas biopsy may play a role in “atypical” DIPG in order to rule out alternate diagnoses. Additionally, as more molecularly specific treatments are developed, the likelihood that biopsy may alter treatment and the need for biopsies for this reason should increase. The information gained

through the biopsy and characterization of these tumors could prove critical to a better understanding and treatment of these neoplasms. Although many neurosurgeons would not biopsy a “typical” DIPG, considerable variability exists between pediatric neurosurgeons as to whether an individual case is typical or atypical and whether or not they would consider biopsy of a lesion.²⁴ A range of biopsy approaches are used depending on tumor characteristics and surgeon preference, including stereotactic suboccipital–transcerebellar biopsy, stereotactic supratentorial–prefrontal biopsy, and open biopsy.^{24,25} Most historical series investigating risk of biopsy were done with computed tomography (CT)–guided imaging. They suggest a 0 to 4% mortality rate, a 0 to 4% permanent morbidity rate, and a 0 to 28% transient morbidity rate.^{26–32} The most recent study suggests 0% mortality, 0% permanent morbidity, and 8% transient morbidity.³¹ Today, MR imaging–guided biopsy has replaced CT-guided biopsy. With MR imaging–guided stereotactic biopsy, the risk for mortality and morbidity was recently estimated to be between 0 and 6%.¹⁸ Of note, parents of children with DIPG seem to be willing to allow biopsy, with a recent study showing that 24% of parents would consent to biopsy for the sole benefit of future treatment development without any direct benefit to their child and that 55% would consider biopsy if there were only a slight chance of benefit.¹⁸ Thus, given the low morbidity of biopsy with current stereotactically guided techniques, biopsy may increasingly be indicated as part of clinical trials and as an aid to treating patients with specific molecular therapeutics. Additionally, biopsy may be indicated in diffuse lesions with atypical features in order to rule out other types of brainstem lesions that may be more amenable to resection or other therapy.

Radiation and Chemotherapy

Standard conventional radiation therapy consisting of daily fractions given 5 days a week for up to 6 weeks is the standard of care for DIPG, with a total dose of approximately 54 Gy.^{1,2,16,18} Most literature suggests the prolongation of progression-free survival but not overall survival with radiation, although a recent study suggested a small survival benefit in patients treated with radiation.^{7,33,34} Hyperfractionated and hypofractionated regimens have not shown any significant benefit in overall

survival when compared with standard conventional radiotherapy.^{1,7,18} The risk for brainstem injury appears to increase at doses greater than 64 Gy.¹⁸ Overall, radiation has an 85% clinical response rate but only a 50% radiologic response rate.¹ The clinical and radiologic responses do not directly correlate, and the relevance of the radiologic response is not clear.¹ Additionally, for most patients, radiation provides only a transient improvement or stabilization of symptoms, with progression of disease about 8 to 9 months after diagnosis.^{16,18} Once tumors progress, there is a tendency for rapid deterioration, with the median time between progression and death ranging from 1 to 4.5 months.¹ A recent study also suggested that radiation had similar effectiveness when delayed by upfront chemotherapy.³⁵

Most studies of chemotherapy for brainstem lesions have focused on DIPG, yet chemotherapy has not been shown to offer a clear survival benefit when used alone or in conjunction with radiotherapy in these tumors.¹ Assessment of chemotherapy results has also been limited by varying patient populations and criteria for response in the different trials, making a comparison of results difficult.¹ One study suggested a possible benefit of chemotherapy in patients in the HIT-GBM database (primarily a German database). The study found that patients treated with chemotherapy showed an increased median survival compared with those treated without chemotherapy, yet most patients who did not receive chemotherapy also did not receive radiation. When only patients treated with irradiation were included, patients treated with chemotherapy and radiation did have a longer survival than those treated with radiation alone.³⁴ However, this study included patients treated with several different chemotherapy regimens, and it is not clear whether the populations of patients who received chemotherapy and who did not are comparable. Another study, which demonstrated the longest published median survival of 17 months, suggested that preradiation chemotherapy may extend survival.³⁵ In this study, BCNU (bischloroethyl-nitrosourea), cisplatin, and in some patients tamoxifen were alternated with two courses of high-dose methotrexate before radiation. Patients then received standard radiation with concurrent hydroxyurea. However, the cost of chemotherapy was high, with significantly longer hospital stays and multiple serious infections.³⁵ Additionally, the patient cohort had a mean duration of symptoms of approximately 2 months before the initiation of therapy, and a longer prodrome has been associated with better survival. Further clinical trials with varying chemotherapy regimens are currently under way.

Future directions include chemotherapeutic agents or therapy with specific molecular targets and the stratification of chemotherapy based on the presence of these targets in a patient's tumor. Two recent Phase I studies of imatinib used this strategy. Imatinib (Gleevec/Glivec; Novartis, East Hanover, NJ) inhibits PDGFR, ABL, and c-KIT tyrosine kinases by inhibiting the adenosine triphosphate (ATP)-binding site. These studies looked at KIT, PDGFRA, and PDGFRB expression in the tumors of patients who were then treated with imatinib.^{36,37} Although neither study demonstrated a clear response of tumor to drug, both had individual patients with stable disease, and they provide an important blueprint for testing chemotherapeutic agents in conjunction with assessing the presence of their molecular target. A previous Phase I trial of imatinib without molecular stratification also had two patients who appeared to respond, but

the majority of patients did not exhibit a response.³⁸ The molecular status of these two patients is unknown. Of note, imatinib has poor penetration of the blood-brain barrier; the second-generation tyrosine kinase inhibitor dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY) shows much better permeability.³⁷ Another molecularly targeted therapy, gefitinib (ZD1839, Iressa; AstraZeneca, Wilmington, DE), an EGFR tyrosine kinase inhibitor, was recently tested in a Phase II study, and patients treated with this agent appeared to show slightly more positive survival and progression-free survival rates than those of historical controls.³⁹ Given the variability of brainstem tumors, it is impossible to determine whether the children in this study are similarly representative of those in historical studies. Thus, the effect could be either over- or underestimated. However, these patients did not undergo biopsy, so EGFR expression in the tumors treated is not known, raising the possibility that the results might improve significantly if only patients with EGFR expression were treated. EGFR can also be targeted via monoclonal antibody, and nimotuzumab, a humanized anti-EGFR monoclonal antibody, appears promising in preliminary clinical studies.⁴⁰ Future trials should focus both on molecular stratification and efficient delivery of chemotherapeutic agents in order to achieve the best results. Additionally, combinations of molecularly targeted chemotherapies may be more beneficial than treatment with individual agents.

Therapeutic Advances (Molecular Characterization, Vaccine Therapy, Convection-Enhanced Delivery)

Understanding the biology of DIPG and other brainstem tumors is an important step in developing more effective treatments. Most research on brainstem tumors has been focused on DIPG, given its grim prognosis; however, the study of DIPG has been limited by a lack of tissue due to the difficulty of operating in this area. Brainstem biopsies were first suggested in the late 1970s and 1980s, but by the 1990s, biopsies were discouraged in typical cases of the disease. Consequently, tissue samples have primarily been restricted to autopsy samples. However, recently some progress has been made in defining the molecular characteristics of DIPG. This is critical for deriving appropriate chemotherapeutic strategies. Previously tried drugs have primarily been those used for adult glioblastoma, but DIPG appears to have distinct biological differences from adult glioblastoma multiforme and even from pediatric supratentorial high-grade glioma,⁴¹⁻⁴³ with the exception of some cases of pediatric midline/thalamic supratentorial high-grade glioma, which may have some similarities.⁴³

Zarghooni et al undertook whole-genome profiling of 11 patient samples of DIPG. Their results may not be fully representative because these were primarily autopsy specimens. Nonetheless, some important molecular characteristics of DIPG began to emerge. In their study, 50% of DIPG samples showed gain of *PDGFA* or *PDGFRA*. Additionally, all samples showed expression of PDGFR- α and downstream target phospho-mTOR (mammalian target of rapamycin).⁴¹ Becher et al similarly found a high rate of expression of PDGFR- α in high-grade brainstem glioma samples, with 87.5% of surgical samples and 50% of autopsy samples showing immunopositivity (overall rate, 67%).⁴⁴ Paugh et al found gains of receptor tyrosine kinases in 56% of their

DIPG samples and reported that gains of *PDGFRA* were seen in 30%. They found overexpression of *PDGFRA* in tumors with amplification and even in a subset of tumors without amplification.⁴² These results suggest that the PDGF pathway may play an important role in DIPG. This is further supported by the induction of brainstem gliomas in mice through overexpression of *PDGF* in the posterior fossa, and the establishment of a PDGF-induced brainstem glioma mouse model that recapitulates many of the features of brainstem glioma.⁴⁴ Other receptor tyrosine kinases seen to have recurrent gains in DIPG (although with a lower frequency than *PDGFRA*) are *MET*, *IGF1R*, *ERBB4*, and *EGFR*.⁴² Of note, overexpression of *IGF1R*, *PDGFRA*, and *EGFR* has also been seen in cases without amplification of the genes.^{41,42} The role of the *EGFR* pathway is less clear, with one study suggesting that it is less frequently involved in DIPG than in adult supratentorial glioblastoma multiforme, and another study suggesting that *ERBB1* is amplified and overexpressed in high-grade DIPG samples.^{41,45} Additionally, another recent series with a small number of samples found that 40% of samples demonstrated expression of epidermal growth factor receptor variant III (*EGFRvIII*), the most common variant of *EGFR*, which is expressed in many tumor samples but rarely in normal tissue.⁴⁶ This finding has been used as the basis for a Phase I trial of an *EGFRvIII* peptide vaccine (a vaccine previously trialed in adult patients with glioblastoma multiforme) after conventional radiotherapy in patients with DIPG.⁴⁶

Genomic analysis suggests that the transcription factors and genes associated with developmental processes are most significantly differentially expressed in DIPG versus cerebral pediatric high-grade glioma. In particular, members of the *HOX* family, critical genes for correct development, including *HOXA3*, *HOXA2*, *HOXD3*, *HOXB2*, and *HOXD4*, show significantly higher expression in DIPG.⁴² Loss of heterozygosity analysis has suggested that mutations in DNA repair pathways may also play an important role in DIPG, and poly (ADP-ribose) polymerase-1 (*PARP1*), a DNA repair gene that is critical for tumor survival in patients with compromised DNA repair ability, was gained in several tumor samples.⁴¹ *PARP* protein was seen to be expressed in additional samples, and *PARP* inhibition could be a potential therapeutic target.⁴¹

One study looking at genetic alterations found that loss of 11p, 17p, 14q, 18p, and 22q was more frequent in DIPG than in pediatric supratentorial high-grade gliomas. Gains of 17q and 10p were unique to DIPG, whereas gains of 1q and 9q were common to DIPG and pediatric high-grade supratentorial gliomas in other locations.⁴¹ Another study with a larger number of samples found DIPG had more frequent gains of chromosomes 2q, 8q, and 9q and losses of 16q, 17p, and 20p than non-brainstem glioblastoma. Chromosome 7 gain and 10q loss were comparable in DIPG and non-brainstem pediatric glioblastoma but less frequent than in adult glioblastoma multiforme, and gain of 1q was similar in DIPG and pediatric glioblastoma multiforme but more frequent in both than in adult glioblastoma multiforme. Loss of 13q and 14q was similar in glioblastoma multiforme in all ages and locations.⁴² A third study showed that loss of 17p and 14q was more common in DIPG than in pediatric high-grade glioma, and gain of 1q was seen at approximately similar rates in both DIPG and pediatric high-grade glioma.⁴⁷ These studies share the findings that loss of 17p is more common in DIPG than in other gliomas and that gain of 1q is

common to both pediatric DIPG and supratentorial glioblastoma multiforme. Of note, 17p is the location of the *TP53* tumor suppressor gene.

Puget et al recently published their results analyzing DNA and RNA from 32 and 23 patients, respectively, with biopsies taken at time of initial diagnosis, the largest sample size to date.⁴³ They suggest that DIPG can be subdivided into two groups that, although different from adult glioblastoma multiforme, have similarities to the proneural and mesenchymal variants of glioblastoma multiforme, respectively. The first group is characterized by overexpression of oligodendroglial markers and strong expression of *Olig2* by immunohistochemistry. The gene expression profile of this group was significantly enriched for *PDGFRA* and the genes associated with this receptor. Additional receptor tyrosine kinases were sometimes also amplified. The survival of this group was significantly worse than that of the second group; 70% of children died before the median overall survival of 10.6 months, whereas 10% of the second group died before this median survival. When samples were compared based on histology alone (allowing the inclusion of 55 samples), patients with oligodendroglial features had a 7.73-month overall survival, compared with a 12.37-month survival for those who had primarily astrocytic features. DIPG in the patients in group 2 was characterized by the upregulation of mesenchymal transition genes, including master epithelial-mesenchymal transition regulators *SNAI1* and *SNAI2/Slug* genes, overexpression of proangiogenic genes, endothelial proliferation, and activation of the *HIF1A* pathway. Group 2 tumors had a higher expression of *STAT3*, a gene whose elimination promotes neurogenesis and inhibits astrogenesis, and these tumors also appeared to be more similar to fetal neural stem cells.⁴³ Additionally, numerous homeobox genes and genes in the sonic hedgehog pathway were found to be overexpressed in brainstem gliomas as opposed to supratentorial high-grade gliomas, and *LHX2* and *IRX2*, two genes that have been described to be preferentially overexpressed in posterior fossa pilocytic astrocytoma and ependymoma compared with supratentorial tumors of the same histology, were also seen to be overexpressed in DIPG compared with supratentorial high-grade glioma. This suggests that there may be gene expression profiles in glial tumors related to the location of origin regardless of histologic diagnosis,⁴³ an idea first proposed for ependymoma and pilocytic astrocytoma. Recently, Monje et al suggested that a nestin + /vimentin + /*Olig2* + cell population in the ventral pons may be the cell of origin of DIPG and that a similar cell population in mice was increased upon upregulation of the sonic hedgehog pathway.⁴⁸

The most recent avenue of genetic research involves a focus on histone H3 mutations. Histone lysine methylation is thought to play an important role in regulating gene expression and chromatin function, and H3.3 is the major histone associated with chromatin during brain development. Two recent studies demonstrated that more than 70% of DIPGs had a lysine-to-methionine mutation on histone H3.3 (K27M-H3.3) or the related H3.1.^{49,50} Additionally, it was found that patients with the K27M-H3.3 mutation have a significantly worse prognosis than patients with wild-type H3.3, and that *PDGFRA* gain or amplification is seen only in patients with this mutation, suggesting that histone mutation is an early event in the development of DIPG.⁵⁰

An additional avenue of research is that of improving therapeutic delivery. The effectiveness of the systemic delivery of chemotherapy for brain tumors is significantly inhibited by the blood–brain barrier. Even a drug that is effective in the laboratory against glioma may not achieve high enough concentrations in the brainstem to have an effect. Thus, research addressing improved delivery to the brainstem is critical, in addition to research investigating improved chemotherapeutic agents. One such delivery method is interstitial infusion, or convection-enhanced delivery (CED). In this method, an agent, such as an antibody- or tumor-targeted toxin, may be infused through a small cannula directly inserted into a tumor in order to deliver the agent throughout the tumor. Brainstem tumors, with their focal location and poor prognosis, seem an ideal target for this therapy.⁵¹ Studies in rats and primates have suggested that agents can safely be delivered to the brainstem via CED.^{52–54} Additionally, a radiation-induced recurrent glioblastoma in the brainstem of a patient in Japan was found to regress after CED of nimustine hydrochloride.⁵⁵ Currently, clinical trials are under way to determine the safety and efficacy of delivering specific agents via CED in pediatric patients with DIPG.

Overall, a new understanding of the biology of brainstem tumors will help in the development of improved therapeutics, and stratification based on tumor biology may help identify subsets of patients who might benefit from currently available therapies. The combination of research into new therapeutics and new delivery methods offers the best hope of an improved treatment strategy for these currently challenging tumors.

42.2.3 Focal Brainstem Tumors

Focal brainstem tumors may be located anywhere within the brainstem but are not usually located within the ventral pons. Focal tumors have well-defined margins typically best appreciated on T2 or FLAIR imaging and occupy less than 50% of the axial diameter of the brainstem.²² They are typically hypointense on T1 imaging and hyperintense on T2 imaging, and they have variable contrast uptake. They may be solid or cystic; however, the area of tumor identified on T1 imaging is usually equivalent to the area identified on T2 imaging.⁵⁶ Focal tumors may present with headache, diplopia, swallowing difficulties, long tract signs, or other cerebellar or cranial nerve dysfunction depending on their location. Symptom duration is typically longer for low-grade tumors and shorter for higher-grade tumors. Focal brainstem gliomas are typically pilocytic astrocytomas or other low-grade gliomas.^{22,57} Less frequently, they may be gangliogliomas or high-grade gliomas.^{22,57}

Surgical Treatment

An attempt at surgical resection should be considered for tumors that are clearly focal on imaging. The surgical approach must be tailored to the location of tumor. A study of 34 patients with focal brainstem lesions undergoing surgery demonstrated 0% postoperative mortality, 15% morbidity, and symptom improvement in 65% of patients.⁵⁶ The selection of patients with clearly focal tumors and surgeon experience are both key to minimizing surgical morbidity. Neurophysiologic monitoring is also helpful in facilitating resection. For patients with tumors

that are not clearly characterized as focal or diffuse through MR imaging, one strategy is to perform stereotactic biopsy and subsequently consider resection if the pathology demonstrates pilocytic astrocytoma, other low-grade astrocytoma, or ganglioglioma.

Radiation and Chemotherapy

Radiation or chemotherapy may be indicated for patients with unresectable lesions or for those with residual tumor after subtotal resection. Gamma knife radiosurgery has also been used to treat focal lesions; one study of 20 patients demonstrated an 84% progression-free survival rate at 5 years.⁵⁸ However, the mean duration until tumor shrinkage was 14.8 months. Tumor response was correlated with higher Karnofsky performance score, higher peripheral dose, smaller tumor volume, and longer symptom duration before radiation on univariate analysis and with Karnofsky performance score alone on multivariate analysis.⁵⁸

42.2.4 Dorsal Exophytic Tumors

Dorsal exophytic tumors are frequently found within the medulla, although they may also arise from the pons and pontomedullary junction. They protrude from the brainstem dorsally into the fourth ventricle. On MR imaging, they typically are hypo- or isointense on T1 and hyperintense on T2, and they show contrast enhancement (► Fig. 42.3).¹² Patients frequently present with signs and symptoms attributable to hydrocephalus, such as failure to thrive or headache and vomiting, and are more likely to have a longer symptom duration before diagnosis than patients with other types of brainstem tumors.¹² Papilledema, nystagmus, and cranial nerve dysfunction are also common findings. Long tract signs are not typically seen. Histology typically demonstrates low-grade (World Health Organization [WHO] grade I or II) astrocytomas or gangliogliomas.^{2,12}

Surgical Treatment

Attempted resection is indicated for dorsal exophytic tumors, and the prognosis is thus significantly better than that for diffuse or focal tumors. These tumors are typically approached through a midline suboccipital craniotomy. The goal is to debulk the exophytic component; however, a gross total resection is often precluded by an indistinct tumor–brainstem interface on the anterior aspect of the tumor (► Fig. 42.3e). Ultrasonic aspiration facilitates debulking. In addition, neuromonitoring is a critical tool in order to allow a safer resection. Neuromonitoring typically includes motor, sensory, and brainstem evoked potentials. Stimulation for cranial nerves allows the differentiation between tumor and brainstem nuclei and helps determine which tissue may safely be removed during surgery. In addition to resection, some patients with dorsal exophytic tumors require surgical intervention to treat resulting hydrocephalus. Because residual tumor is frequently left, patients may require repeated debulking surgery at the time of regrowth of the tumor. Repeated surgery appears to be an effective option for controlling regrowth, and tumors appear to be of similar histology upon regrowth.⁵⁹

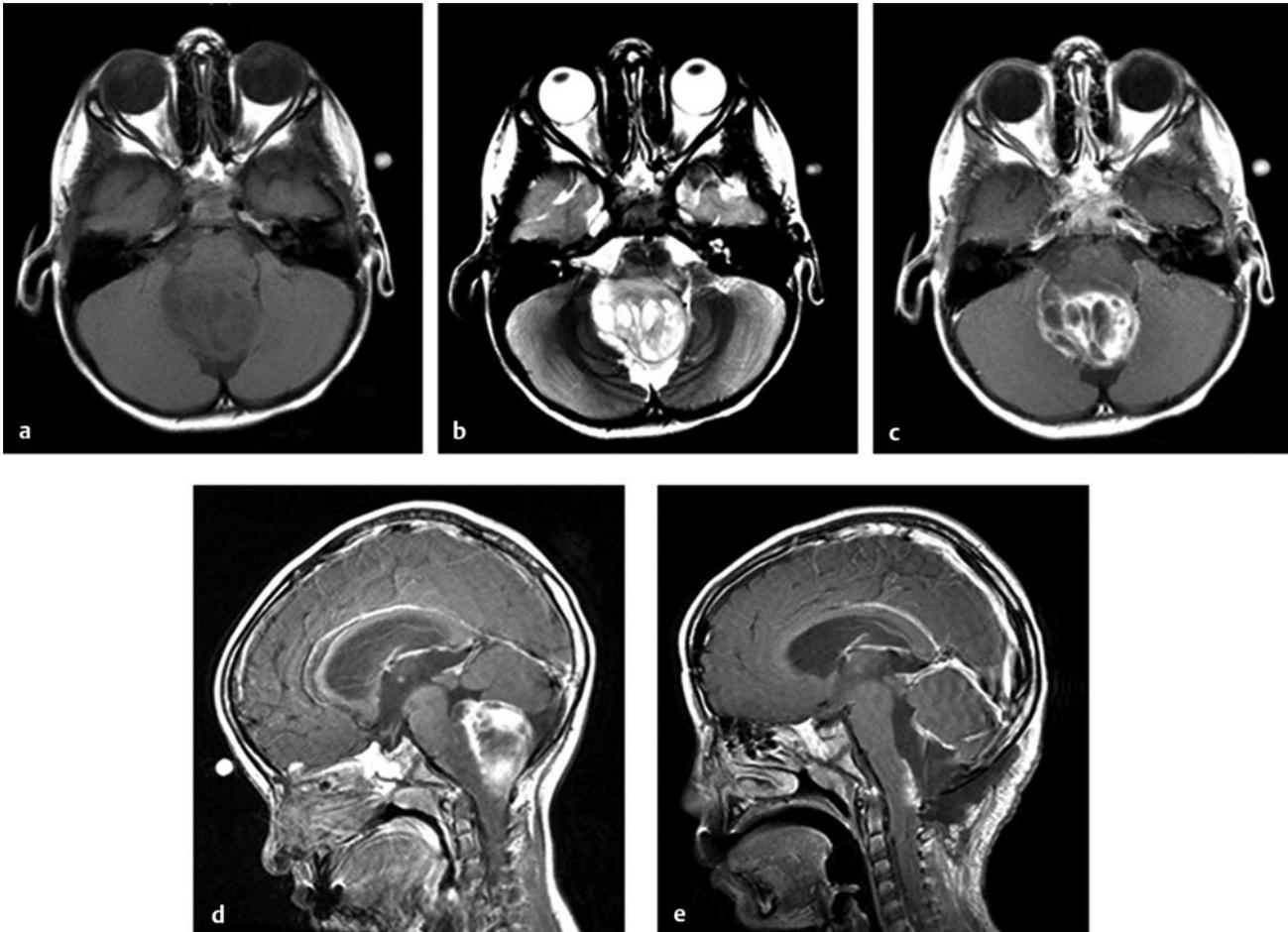


Fig. 42.3 Dorsal exophytic brainstem tumor. (a) Axial T1-weighted magnetic resonance (MR) image of a child with a dorsal exophytic brainstem tumor demonstrating dorsal extension of the tumor. (b) Axial T2-weighted MR image of the same patient. (c) Axial and (d) sagittal T1-weighted MR images with gadolinium contrast demonstrating contrast enhancement, as is typical of this type of tumor. (e) Sagittal T1-weighted MR image with gadolinium contrast of the same patient after resection. Most of the exophytic tumor could be resected. However, these tumors typically have a poorly demarcated interface with the brainstem, so that a small amount of tumor must be left to prevent injury to the brainstem. Note the area of contrast enhancement representing residual tumor on the dorsal surface of the brainstem.

Radiation

Although surgery is the treatment of choice, focused radiation may be used for residual disease in cases of subtotal resection.

42.2.5 Cervicomedullary Tumors

Cervicomedullary tumors often appear similar to upper cervical cord tumors, with behavior more similar to that of spinal cord astrocytomas than that of brainstem gliomas. In these patients, the tumor appears to arise from the cervical cord, with rostral growth limited by the medullary decussation. Margins in these tumors are typically more distinct, with symptoms caused by compression of brainstem fibers rather than infiltration. However, other cervicomedullary tumors behave more like infiltrating tumors of the medulla with caudal extension into the spinal cord. These tumors are more difficult to treat because they have much less distinct margins.⁶⁰ Children with both types of cervicomedullary tumors typically present with bulbar symptoms, focal neurologic deficits of the lower cranial nerves, or long tract signs.

The pathology of cervicomedullary tumors is frequently low-grade glioma but can also be ganglioglioma, anaplastic astrocytoma, or ependymoma.⁹

Surgical Treatment

Cervicomedullary tumors are typically approached through a midline suboccipital craniotomy with cervical laminectomy as needed for cervical exposure. For tumors with distinct margins, complete resection may be possible. However, frequently biopsy or subtotal resection may be more appropriate given their infiltrative (WHO grade II) nature. Neuromonitoring, such as that described above, is typically used to aid resection.

Radiation and Chemotherapy

Radiation or chemotherapy is used in patients who undergo subtotal resection or in whom resection is not possible. The timing of adjuvant therapy and choice of modality depend on the treating oncologist and age of the child. Chemotherapy and radiation may also lead to an increased definition of the

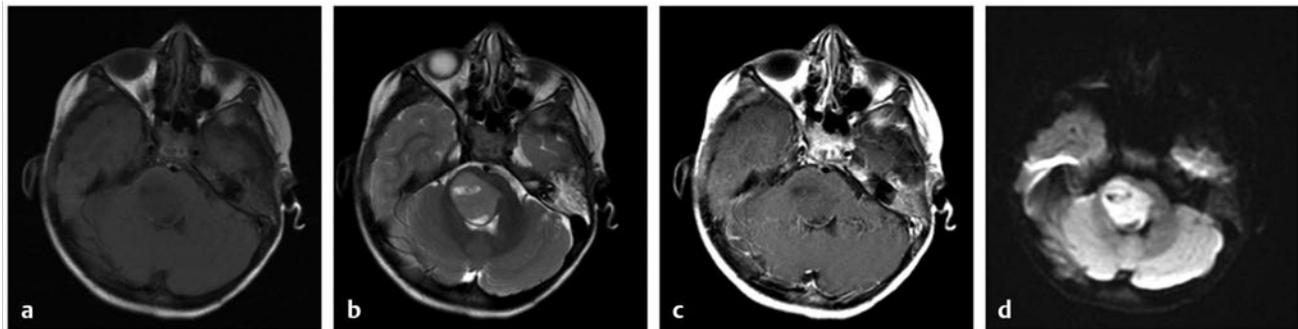


Fig. 42.4 Primitive neuroectodermal tumor (PNET) of the brainstem. (a) Axial T1-weighted magnetic resonance (MR) image of a child with histologically confirmed PNET. (b) Axial T2-weighted MR image of the same patient. (c) Axial T1-weighted MR image with gadolinium contrast. Unlike PNETs in other locations, PNETs in the brainstem typically do not demonstrate contrast enhancement. (d) Axial diffusion-weighted MR image demonstrating diffusion restriction. This finding is typical for PNETs and may help discriminate them from other types of lesions in this area.

brainstem–tumor interface and thus facilitate surgery after adjuvant therapy.⁶⁰

42.2.6 Additional Considerations: Primitive Neuroectodermal Tumors

PNETs may rarely be found in the brainstem. They typically appear as well-circumscribed focal pontine tumors with hypointensity on T1 imaging and hyperintensity on T2 imaging (► Fig. 42.4).⁶¹ Unlike PNETs in other locations, contrast enhancement is usually absent in brainstem PNETs. They often show leptomeningeal spread, and an exophytic appearance is common although variable in degree. Hydrocephalus is also typically present in children with PNETs at the time of diagnosis. The median age of this subpopulation of patients with brainstem tumors appears to be younger than that of typical patients with DIPGs; the average age of patients with brainstem PNETs was 2.7 years in one series.⁶¹ Patients with the appearance of PNETs on MR imaging should undergo biopsy to confirm the diagnosis and resection if possible. Spinal imaging should be obtained in patients with PNETs to determine the extent of leptomeningeal spread, and radiation to the entire craniocervical axis should be considered.

42.3 Prognosis

The prognosis for children with DIPG is extremely poor; the prognosis for children with other subtypes of brainstem tumors is significantly better. In most studies, the survival rate for DIPG is less than 10% at 2 years, with a median survival time of less than 1 year.^{1,16,19,34} In contrast, other brainstem tumors that may be amenable to surgery have a much better prognosis. Sandri et al described an 87.4% rate of 4-year survival and a 58.8% rate of 4-year disease-free survival for nondiffuse tumors, with the most important prognostic factor being extent of resection.¹⁶ Fried et al similarly described a very favorable outcome for brainstem low-grade tumors (a category that includes low-grade tumors of multiple subtypes, described above). In their study, patients with brainstem low-grade tumors had a 5-year progression-free survival of $57\% \pm 3\%$ and an overall survival of $89\% \pm 5\%$.⁶² Fisher et al noted a significant difference in survival based on pathology, with a $95\% \pm 5\%$ -year survival for pilocytic

astrocytomas versus a $23\% \pm 11\%$ 1-year overall survival for fibrillary astrocytomas.⁵⁷

Studies have shown that age younger than 2 years, the presence of cranial nerve palsies (particularly abducens palsy), long tract signs on presentation, a pontine location, encasement of the basilar artery, and a shorter duration of symptoms before diagnosis predict a poor outcome.^{19,57} Patients with neurofibromatosis, an older age, and a longer duration of symptoms before diagnosis are thought to have a more favorable outcome.^{16,19}

Pearls

- Brainstem gliomas are a diverse group of tumors with widely divergent treatment strategies and prognoses, and the likelihood of high-grade pathology and a poor prognosis is very well predicted by location, appearance on MR imaging, and symptoms.
- DIPG is currently primarily treated with radiation; there is little role for surgery.
- Given the poor prognosis of patients with DIPGs, much work is currently being directed at understanding the biology of these tumors and producing better treatment options.
- Tectal, focal, dorsal exophytic, and cervicomedullary tumors are typically low-grade and may be amenable to resection. In many cases, patients have a reasonably good prognosis.

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43 Cerebellar Astrocytomas

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Except in infants and very young children (younger than 1 year), the posterior fossa is the most common site of occurrence for pediatric primary brain tumors.¹ Of the tumors occurring in this location, medulloblastoma is the most common, accounting for 35 to 50% of cases and presenting mainly in the first decade of life,^{2,3} followed by cerebellar astrocytomas, which can develop throughout childhood and into early adulthood.^{4,5} Historically associated with a favorable outcome, individual cerebellar astrocytomas in reality can display different behaviors, depending mainly on the presence or absence of invasion, extent of surgical resection, and histologic grade. An understanding of the natural history of the disease, as well as the available therapeutic options, is necessary to achieve the best outcome in each case.

43.1 Epidemiology

Cerebellar astrocytomas occur most often in the pediatric population, with 70 to 80% of cases developing in children.^{6,7} They account for 10 to 20% of all pediatric brain tumors^{2,7} and up to 25 to 35% of posterior fossa tumors in children,^{6,8} with an incidence of 0.3 to 0.4 cases per 100,000 children per year.⁸ The mean age at diagnosis is 6 to 7 years^{7,9,10} when patients younger than 18 years are considered, and it is 17 to 18 years when adult cases are taken into account.⁷ Only 3% of cases have been reported in children younger than 1 year.¹¹ Whereas medulloblastoma more frequently affects males, cerebellar astrocytomas show no evidence of a gender predilection.^{5,7,9,10} Historically, pilocytic astrocytoma has been reported as the most frequently occurring tumor, accounting for 70 to 80% of cases, followed by low-grade diffuse astrocytoma (10 to 15%) and higher-grade tumors, such as grade III anaplastic astrocytoma and grade IV glioblastoma multiforme (5%).^{6,12,13} However, if the recently described new entities, such as pilomyxoid astrocytoma and “diffuse” pilocytic astrocytoma (see below), are taken into account, up to 95% of all cerebellar astrocytomas consist of pilocytic and pilomyxoid variants, whereas the remaining 5% consist of diffuse astrocytomas of both low and high grades.¹⁴ The cerebellum is the most common location for pilocytic astrocytoma in children,¹⁵ except in patients affected by neurofibromatosis type 1 (NF-1), in whom cerebellar involvement occurs in fewer than 1% of cases.¹⁶

43.2 Pathology

43.2.1 Gross Appearance

Pilocytic Astrocytomas

Pilocytic astrocytomas (PAs) are very common World Health Organization (WHO) grade I tumors. They grow slowly and have a relatively low propensity for parenchymal infiltration. Often, cerebellar PAs invade the subarachnoid space, but this is not associated with an increased risk for cerebrospinal fluid (CSF) spread or a worse prognosis.¹⁷ Distant leptomeningeal dissemination has been occasionally described and may be (although not

always) associated with a worse prognosis, as long-term survival occurs even without ancillary therapy.^{14,18–21} Thus, CSF dissemination may indicate, for example, simple chance fragmentation and dispersal of tumor already present in the subarachnoid space. PAs usually appear gray to tan–pink and may have pronounced vascularity.¹⁷ Tumor consistency varies from very soft and gelatinous to firm and rubbery (rarely, rock-hard). Lesions in the cerebellar hemispheres often show one or more macrocysts^{10,11} filled with proteinaceous fluid and delimited by a cyst wall that can be either neoplastic or formed by reactive gliosis.^{7,10,22} Macrocysts may occur adjacent to tumor or within tumor. The tumor often appears as a solid mass (“mural nodule”) in the cyst wall. Tumors of the vermis or fourth ventricle are usually less macrocystic.¹⁰ Some PAs appearing to “arise within” the fourth ventricle are actually dorsal exophytic growths from the brainstem that enter the fourth ventricle through the outflow foramina. Calcification occurs occasionally. Hemorrhage also occurs occasionally, and evidence of prior hemorrhage is the presence of perivascular hemosiderin pigment. In a rare case, acute hemorrhage may occur into a macrocyst, causing sudden decompensation with increasing mass effect and intracranial pressure (ICP), edema, herniation, and death.

Pilomyxoid Astrocytomas

Pilomyxoid astrocytomas (PMAs) were characterized in 1999.²³ This tumor was included in the 2007 WHO classification as an independent grade II entity, particularly because of its tendency to more aggressive behavior compared with PA.¹⁴ PMAs are most often seen in the first 2 to 3 years of life and occur mostly in the midline, especially in the region of the optic chiasm, hypothalamus, and third ventricle; in this midline supratentorial region, PMAs may occur in older children, but cerebellar PMAs are generally limited to those younger than 2 to 3 years old. Currently, PMA is believed to represent a more aggressive “variant” of PA, with a greater tendency to local recurrence and CSF dissemination versus PA. This appears especially true of PMAs that arise in the supratentorial midline.^{14,23} Progression-free survival (PFS) is shorter for PMA than for PA, and “death from disease” is more frequent with PMA. Grossly, PMAs are well circumscribed, solid (a small fraction may have a usually minor cystic component), pale tan–pink, soft, and gelatinous. They may also be partly very soft, pale yellow, and necrotic (a small fraction, but more of them than of PAs).

Diffuse Fibrillary Astrocytomas

Diffuse fibrillary astrocytomas (DFAs) are relatively infrequent WHO grade II, grade III (anaplastic astrocytoma), or grade IV (glioblastoma, glioblastoma multiforme) tumors in the cerebellum. They appear as gray–tan–red, ill-defined, infiltrative lesions, with a consistency ranging from firm to gelatinous. These tumors may display microcystic degeneration, but they usually lack the frank macrocystic appearance of many PAs. Glioblastoma multiforme (GBM) characteristically has central necrosis and may show gross thrombosis of associated larger vessels.

43.2.2 Microscopic Appearance

Pilocytic Astrocytomas

The most classic feature of PAs (► Fig. 43.1) is the “biphasic pattern.” This is characterized by dense pink–red fibrillary regions composed of many spindle-shaped bipolar (piloid) astrocytes with elongated nuclei and very long and thin hairlike processes extending from both tips of tumor cells. These regions alternate with intervening looser areas that represent microcystic and often mucinous degeneration of the tumor (with cellular elements composed predominantly of multipolar rather than bipolar cells, cells resembling “protoplasmic” astrocytes, or even oligodendrogloma-like cells with generally more round to oval nuclei).

Other forms of degenerative change seen in PA include increased numbers of hyalinized (thickened and sclerotic, or scarred) blood vessels, occasionally associated with downstream foci of bland ischemic-type tumor necrosis, possibly related to occlusive events occurring within these abnormal vessels, and often marked yet benign nuclear atypia or pleomorphism; both hyalinized vessels and “degenerative”-type nuclear atypia are common in PA. The latter may appear worrisome (resembling anaplasia to the inexperienced), but these markedly atypical nuclei express no proliferation markers, show no mitotic activity, and occur in a background of otherwise typical features of PA. In addition to increased nuclear atypia, foci of necrosis, and extension into the subarachnoid space, other features that may appear worrisome to the less experienced eye include rare scattered mitotic figures, glomeruloid-type vascular proliferation (usually capillary-size vessels with multiple lumina and often only simple hypertrophic endothelium, but occasionally intraluminal hyperplasia or

multilayering of endothelial-type cells, the latter tending to occur adjacent to macrocysts), and sometimes relatively increased cellularity. None of these aforementioned features have any prognostic significance in PA.^{14,24} Subarachnoid spread of PA is evidenced by a micro-multinodular pattern of growth, with variably thin fibrous septae present between small tumor nodules.

Other often helpful diagnostic features, which alone are *neither necessary nor* sufficient for the diagnosis of PA, include Rosenthal fibers (dense, glassy, hyaline pink–red intracytoplasmic inclusions, seen as corkscrew-shape structures in longitudinal sections or as discrete round to ovoid bodies in cross sections and mainly concentrated in the denser pink fibrillary areas of the tumor) and eosinophilic granular bodies, also intracytoplasmic and round but granular pink–red, raspberry-like protein aggregates, typically better seen in looser microcystic/mucinous foci.^{25,26}

Rosenthal fibers are also seen in reactive (“piloid”) gliosis and thus are not always a sign of neoplasia. In piloid gliosis, the number of Rosenthal fibers present usually is greater than the number of nuclei seen, and microcystic change is also not generally present.

Pilomyxoid Astrocytomas.

The microscopic appearance of PMAs (► Fig. 43.2) is characterized by the following: a markedly predominant to solely (i.e., monophasic) “loose” microcystic/mucinous or myxoid background pattern, without any significant dense fibrillary component; a frequent, characteristic, often prominent vasocentric pattern of tumor cells attaching to and surrounding blood

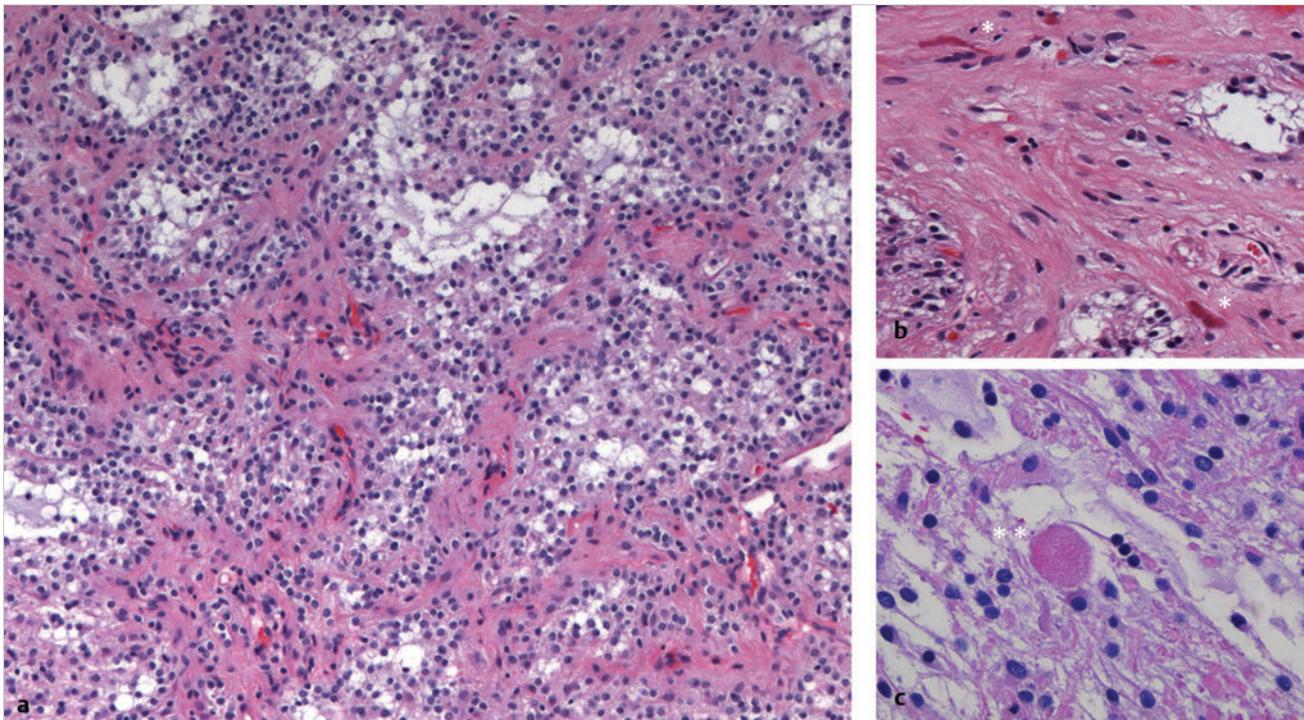


Fig. 43.1 Histologic appearance of pilocytic astrocytoma. (a) Low-power microscopic field after hematoxylin and eosin staining shows the classic biphasic pattern of dense eosinophilic fibrillary areas (pink–red) intermixed with loose mucinous microcystic regions (pale gray–white). (b) At higher magnification, Rosenthal fibers (single asterisks) appear as thick, dense, glassy, and eosinophilic corkscrew-like structures, found mainly in the dense fibrillary areas, whereas (c) eosinophilic granular bodies (double asterisks) appear as round pink granular structures, mainly localized to microcystic areas.

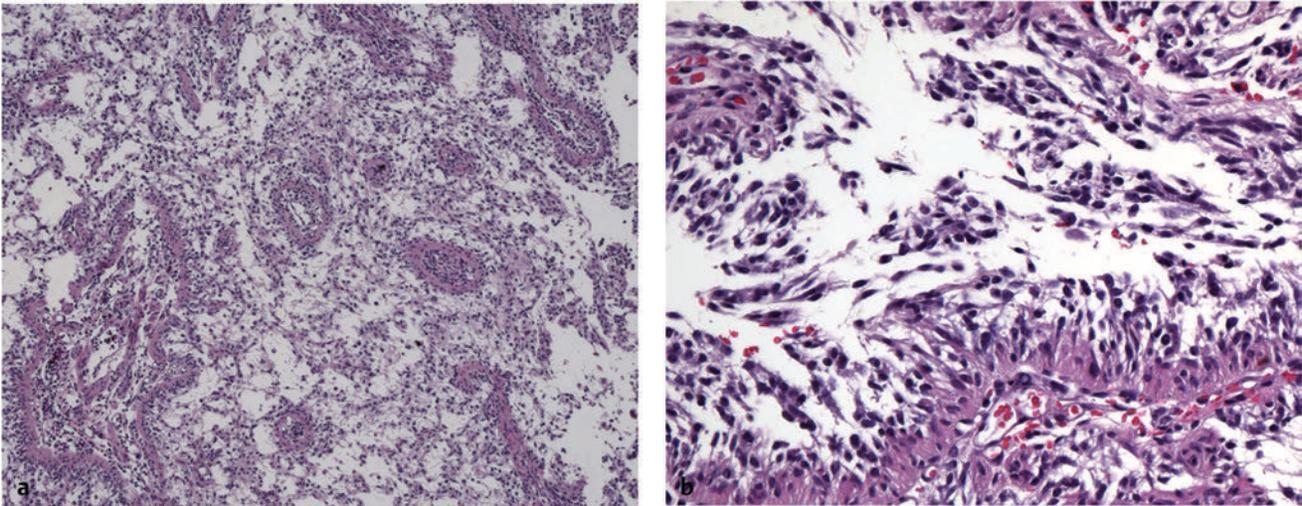


Fig. 43.2 Histologic appearance of pilomyxoid astrocytoma. (a) On low-power microscopy, the tumor is composed of scattered blood vessels within a purely microcystic background, lacking the characteristic biphasic appearance of pilocytic astrocytoma. (b) Characteristic of this tumor is a radial orientation of monomorphous tumor cells adhering to the blood vessel walls; this “angiocentricity” is better visualized at higher magnification. No Rosenthal fibers or eosinophilic granular bodies should be seen.

vessel walls; typically uniform, monomorphic (piloid) bipolar spindle tumor cells; and essentially complete absence of Rosenthal fibers, as well as a severe dearth or absence of eosinophilic granular bodies.^{23,25} Tumor cells are characteristically arranged in a perpendicular fashion around blood vessel walls, revealing a so-called vasocentric or perivascular rosette-like configuration.²⁷ These perivascular collars are usually composed of a single layer of elongated tumor cells, which insert relatively stout processes into the vessel walls. Necrosis is not common but occurs somewhat more frequently than in PA. Calcification is relatively rare in PMA and is occasionally seen in PA. The mitotic index in PMA may be slightly higher than that in PA.²⁵ Occasionally, glomeruloid-type microvascular proliferation may be seen in PMA. Some PMAs appear to “mature” (or perhaps “burn out”) into PAs over time,²⁸ but initial sampling error (i.e., secondary to the receipt of only a small biopsy specimen for pathologic evaluation) may also explain this “phenomenon,” in at least some cases. Much less frequently, the reverse appears to occur (i.e., a PA recurs as an apparent PMA). Whether the latter may occur due to overgrowth of the “loose” component (which often contains tumor cells with a higher overall proliferation index) or results from some sort of transformative event or simply represents sampling error in the initial biopsy is unclear at this time.

Diffuse Fibrillary Astrocytomas

DFA (► Fig. 43.3) are WHO grade II tumors. The major (although variable) features that may help differentiate DFA from PA include more nuclear atypia and hyperchromasia, often less cellularity, and a more homogeneous cellular composition of fibrillary astrocytes (often without a clearly loose/microcystic component).²⁹ The neoplastic cells definitely infiltrate brain. Mitoses should be relatively inconspicuous to absent for this to be classified as WHO grade II.³⁰ Vascularity is much less prominent than in PA and PMA. DFA is much less common than

PA and even PMA in the cerebellum. One helpful finding, which may be seen in smear preparations or sections, may be the increased presence of apoptosis or apoptotic bodies in DFA relative to PA (D.R.B., unpublished observation); otherwise, these two entities (PA and DFA) can be somewhat difficult to differentiate by routine histopathology alone, particularly with smaller samples. Another differentiating feature is that the piloid (long, thin, hair-like) processes typical of PA should not be a prominent feature in cytologic preparations of DFA, but this is not always a readily obvious difference. Most important may be the utilization of radiologic correlation to help differentiate these entities. WHO grade II DFA is nonenhancing and solid (not macrocystic), and it has blurry, infiltrative borders, in contrast to the typically enhancing, macrocystic, and discrete WHO grade I PA. Recently described molecular genetic markers may also be of further help in this differential. The “entity” of “diffuse” pilocytic astrocytoma is also described.^{14,31–33} Most practicing neuropathologists still consider this a WHO grade I neoplasm. This is a PA in which at least some significant portion infiltrates the cerebellum, especially if an infiltrative pattern of growth is noted even within the epicenter of the tumor; infiltration may be best demonstrated by the use of immunohistochemistry with antibodies to neurofilament protein (NFP), which demonstrate many NFP-positive cell processes/axons present within, and especially if present throughout, the specimen. In carefully examined gross total (and other large) resection specimens that are completely or nearly completely submitted for microscopic examination, at least a component of focally “diffuse” or infiltrating pattern is seen in many if not most cerebellar PAs. It is possible for such tumors, when suboptimally examined, to be mistakenly designated as “DFA” and thus “overgraded” as WHO grade II. Recent studies suggest that the biological behavior and overall prognosis for PA and for “diffuse” PA are similar, and that “diffuse” PA does not require any special clinical consideration or intervention in comparison with “classic” PA.^{14,32,33}

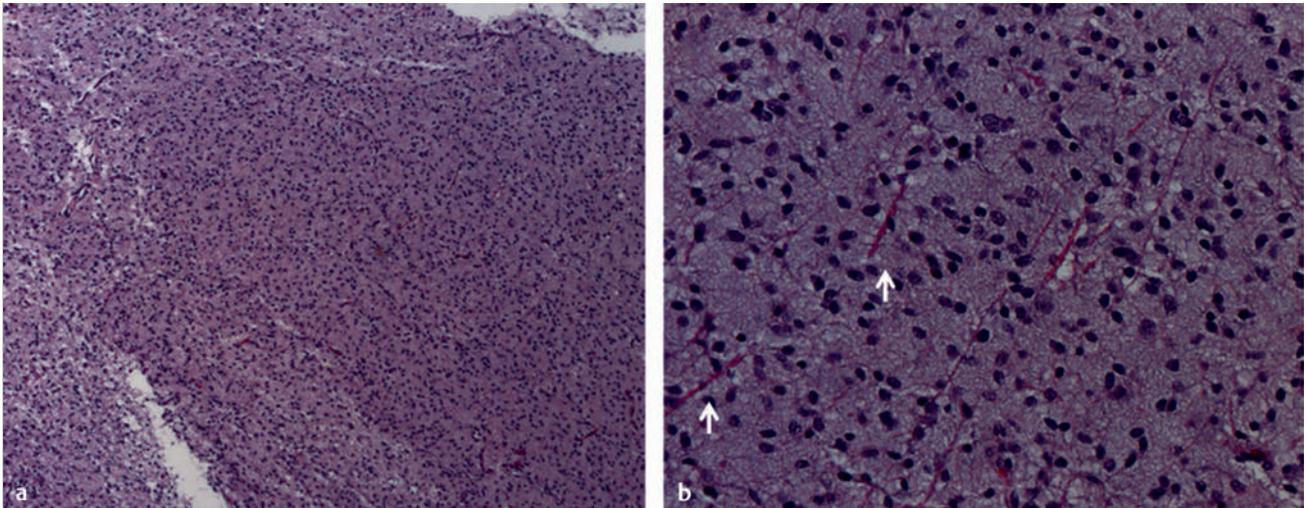


Fig. 43.3 Histologic appearance of diffuse fibrillary astrocytoma (World Health Organization grade II). (a) Low-power microscopy shows a homogeneous cellular pattern, with moderate hypercellularity and minimal pleomorphism and nuclear atypia. At higher magnification (b), it is possible to better observe a background composed of normal (pink) axonal processes (white arrows) demonstrating tumor infiltration into normal tissue. Mitotic activity is not seen.

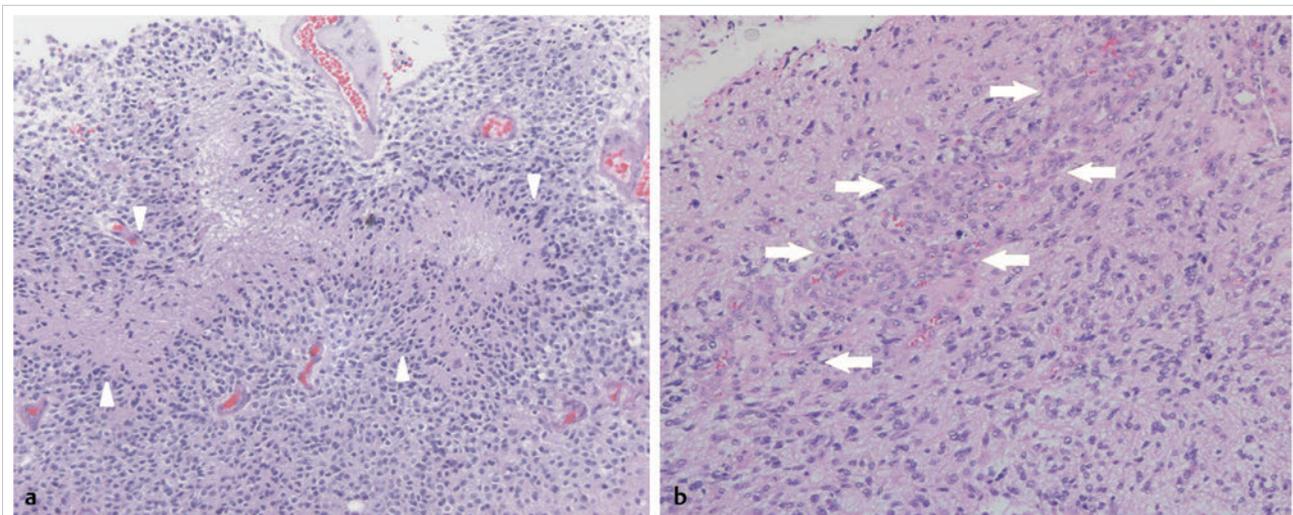


Fig. 43.4 Histologic appearance of glioblastoma multiforme. (a) At low magnification, it is possible to observe the pronounced hypercellularity, nuclear pleomorphism, and characteristic pseudopalisading of viable tumor cells about an area of tumor necrosis (white arrowheads). (b) A focus of vascular endothelial proliferation (white arrows) is causing nearly complete obliteration of blood vessel lumina; this finding (like pseudopalisading necrosis) is pathognomonic for glioblastoma multiforme (differentiating it from anaplastic astrocytoma).

Diffuse Anaplastic Astrocytoma and Glioblastoma Multiforme

These tumors (► Fig. 43.4) are both generally characterized by increased nuclear pleomorphism, hyperchromasia, and increased mitotic activity. Microvascular endothelial proliferation (multilayered “endothelium”) or pseudopalisading necrosis is pathognomonic for GBM.^{13,34} Bona fide “diffuse” (fibrillary, infiltrating) astrocytomas of the cerebellum, although infrequent overall, are more often of a higher grade (WHO grade III or IV rather than WHO grade II).^{14,32}

43.3 Molecular Biology

Because of the frequently benign course of PA after surgical resection, its molecular signatures have not been studied as extensively as those of medulloblastoma, a tumor associated with a much worse prognosis and in need of better alternative therapies. However, the recent notions that not all pediatric cerebellar astrocytomas behave in the same way, that tumor recurrence does happen, and that adjuvant treatments may have to be considered in certain cases have stimulated the need for a deeper understanding of tumor biology.

Pediatric astrocytomas are molecularly different from the other astrocytic tumors that occur in adults. At the cytogenetic level, the karyotype is normal in at least 50 to 70% of cases^{35,36} and in up to 80% when only cerebellar astrocytomas are considered.³⁷ Although adult astrocytomas are often characterized by loss of the short arm of chromosome 17 (17p) and long arm of chromosome 10 (10q), pediatric astrocytomas do not display a consistent karyotypic pattern,³⁸ with the exception of the frequent duplication of chromosome 7q, which has been described in the majority of pilocytic astrocytomas and in 50% of diffuse fibrillary astrocytomas in children. Gain of 7q copy number results in gain of function of the gene *BRAF*.³⁹ Unlike in adult astrocytomas, p53 mutation and loss of *CDKN2A* (p16) are not common findings in pediatric astrocytomas,^{40,41} and *EGFR* amplification is virtually absent.^{38,42}

Among the molecular features that most consistently characterize PAs is the gain of function, by gene duplication, of *BRAF*, a serine/threonine protein kinase that, in turn, activates the MAPK/ERK cascade, leading to cellular proliferation.⁴³ A recent analysis of 49 specimens of PA revealed duplication of the *BRAF* gene in 41 cases (83%), and this was twice as common in cerebellar as supratentorial tumors.⁴⁴ As a proof of the connection to tumor pathogenesis, upregulation of *BRAF* expression in mouse neuroprogenitor cells induced the formation of intracranial PAs in vivo in 91% of cases.⁴⁵ In addition, overexpression of *BRAF* in human neural stem cells induced an initial increase in clonogenic ability and proliferation, which was then followed by progressive cell senescence mediated by activation of p16. This phenomenon, known as oncogene-induced senescence (OIS), is characterized by a paradoxical decrease in cell growth or even total growth arrest initiated by oncogene induction, and it is triggered by the activation of tumor suppressor genes in response to abnormal proliferative stimuli. This observation may explain the often indolent behavior of the majority of PAs and low-grade pediatric astrocytomas, whose cells, although transformed, are still kept under control by the retained expression of major tumor suppressors, including p53 and p16.⁴⁶ This may explain the high percentage of apoptotic cells observed in these tumors,⁴⁷ as the result of the opposed action of proliferative and inhibitory stimuli. Although the association of supratentorial PA with NF-1 has been elucidated, and loss of heterozygosity of *NF1*, the gene encoding the tumor suppressor protein neurofibromin, has been recognized as the hallmark of PAs associated with NF-1, *NF1* mutation has not been observed for sporadic tumors,⁴⁸ suggesting a different molecular origin. A genetic screen comparing NF-1-associated with sporadic PAs revealed 26 genes differentially expressed between the two groups. Of these, *ALDH1L1* expression has been associated with the NF-1-associated histology as well as with the more indolent tumors in general. In particular, *ALDH1L1* downregulation has been found in 89% of PMAs and PAs with atypical features.⁴⁹

With regard to the cell of origin of pediatric astrocytomas, immunostaining for SOX2, a transcription factor associated with “cancer stem cells,” was reported positive in about 10% of cells in 42 of 45 PAs.⁴⁴ This raises the question whether a PA stem cell exists, as demonstrated for medulloblastoma, glioblastoma,⁵⁰ and diffuse pontine glioma.⁵¹ In their seminal work on brain tumor stem cells, Singh et al were able to isolate cells with clonogenic ability from operative explants of PA that were immunoreactive for nestin and CD133, two of

the accepted markers for cellular stemness. However, there has been no validation, to date, that these cells would be able to recapitulate tumor formation in vivo, as has been done for other brain tumors.⁵²

43.4 Clinical Presentation

Posterior fossa tumors in children mainly present with symptoms of increased ICP, regardless of histology. This is due to progressive mass effect leading to obstruction of the fourth ventricle with resulting hydrocephalus, which is present in up to 85% of patients.^{7,10,11,22,25} Headache and vomiting are the two most common symptoms at presentation^{10,22} and are usually more pronounced in the morning because of recumbent position and increased cerebral blood volume secondary to higher PaCO₂.

The presentation also depends on the child's age; in patients younger than 3 years, macrocrania and motor delay are common,¹² whereas in older children, cerebellar signs are prominent and depend on the tumor location. Different from medulloblastoma and ependymoma, which present most commonly with truncal and gait ataxia due to their midline position, astrocytomas frequently present with limb ataxia that is secondary to hemispheric involvement. Papilledema, nystagmus, and diplopia are also frequently observed.^{7,10,11,22}

The time to diagnosis is usually longer than for medulloblastoma because of the slower growth rate of astrocytomas; it ranges from weeks to several months,^{7,10} depending on tumor location. Typically, the symptomatology associated with vermian lesions progresses more quickly than that associated with hemispheric tumors. The sudden onset of symptomatology secondary to intratumoral bleeding has been described.⁵³

43.5 Imaging

Computed tomography (CT) of the head with and without contrast has been historically considered the first diagnostic step for the evaluation of children presenting with symptoms suggestive of posterior fossa pathology (► Fig. 43.5). However, with the exception of the ability to differentiate between astrocytomas and medulloblastomas (decreased X-ray attenuation on unenhanced CT for the former, increased X-ray attenuation for the latter), CT is, in all other regards, inferior to magnetic resonance (MR) imaging of the brain for obtaining an accurate definition of tumor characteristics and anatomy. In our experience, limited MR imaging (axial T2-weighted sequence) serves as a screening examination in symptomatic patients. It can be performed as a safer, fast, and well-tolerated alternative to CT as an initial examination.⁵⁴ If pathology is detected, formal MR imaging of the brain and spine will need to be obtained for surgical planning and prognostication.

Regardless of imaging modality, cerebellar PAs appear as well-demarcated, often sizable lesions occupying the vermis (12.5 to 25%), hemispheres (36 to 40%), or concurrently the vermis and hemispheres (40%).⁵⁵ Radiologically, astrocytomas have been described as presenting with three possible patterns (► Fig. 43.5):

1. Classic cystic astrocytoma presents as a usually large cystic lesion with an enhancing mural nodule but a nonenhancing cyst wall, which is considered nonneoplastic.

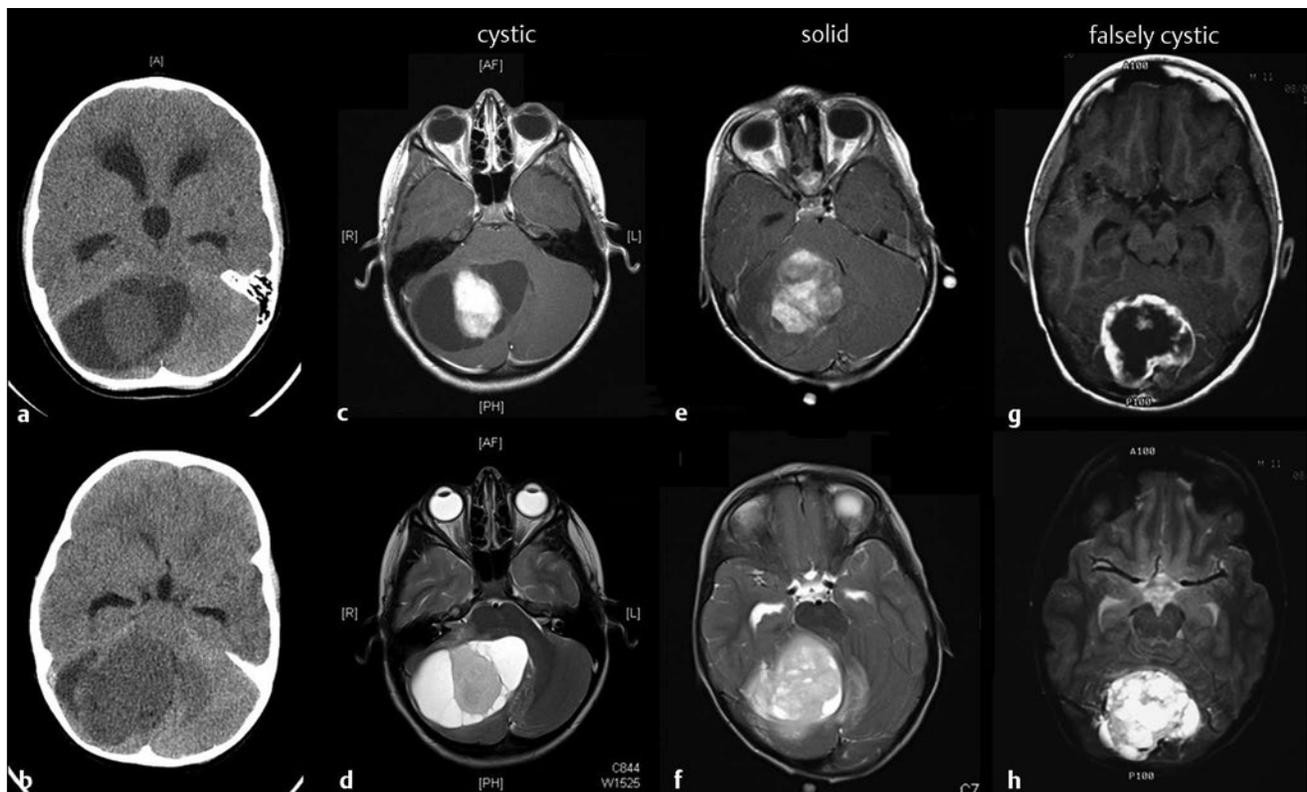


Fig. 43.5 Radiologic appearance of cerebellar pilocytic astrocytoma. Nonenhanced axial computed tomography shows either a hypo- or isodense nodule surrounded by signal, consistent with a fluid-filled cavity (a), or a slightly hypodense and heterogeneous mass in the case of a solid tumor (b). T1-weighted magnetic resonance imaging after the intravenous administration of gadolinium differentiates among “classic” cystic (c), solid (e), and falsely cystic (g) tumors. Neoplastic tissue enhances briskly upon contrast injection. In T2-weighted images, the solid component of the tumor (d,f,h) appears hyperintense to normal brain, a characteristic peculiar to pilocytic astrocytomas.

- False cystic astrocytoma is characterized by the presence of a cystic component within the tumor. The tumor and cyst wall show contrast enhancement. The wall is thicker than 2 to 3 mm and is considered neoplastic.
- Solid astrocytoma is devoid of macroscopic cystic formation and commonly occurs in the vermis.^{7,10,56} Fibrillary astrocytomas usually present as solid masses with less defined borders, suggesting invasion. They most often do not enhance.

Fewer than 10% of PAs invade the brainstem, a behavior more commonly observed with tumors arising in the midline and abutting the fourth ventricle.^{11,57,58} However, the presence and extent of brain stem invasion are usually difficult to predict preoperatively.

On MR imaging, the cystic component of PAs, when present, has a lower T1 signal and a higher T2 signal than that of brain. The mural nodule exhibits increased signal compared with brain on T1 images and enhances brightly and uniformly upon intravenous gadolinium administration. The extent of contrast enhancement of the cyst wall has been considered predictive of its nature; thick enhancement suggests a neoplastic cyst wall, whereas absent or limited enhancement (usually <2 mm in thickness) is more consistent with reactive glial tissue.⁵⁹ However, several authors failed to confirm a strong correlation between radiologic appearance and histology.^{22,60} Solid tumors

usually enhance briskly, but up to 30% of lesions can display areas of decreased or absent enhancement.⁷ Particularly useful for the differentiation between astrocytomas and medulloblastomas are T2 images; the solid component of an astrocytoma consistently exhibits increased signal compared with brain, whereas a medulloblastoma exhibits similar or decreased signal compared with brain.⁶¹ Recently implemented apparent diffusion coefficient (ADC) maps have shown a specificity of 100% in differentiating cerebellar astrocytomas (higher signal intensity) from medulloblastomas (lower signal intensity).⁶² Peritumoral edema is rarely present and does not correlate with prognosis. Intratumoral calcifications are detectable in 25% of cases of PA.⁶³

43.6 Treatment

Cerebellar astrocytoma is a surgical entity, and the primary treatment of cerebellar astrocytomas is surgical resection, with the goal of obtaining total tumor removal. In fact, extent of resection is the main predictor of recurrence and survival.

43.6.1 Preoperative Management

As discussed, children are usually diagnosed when already symptomatic secondary to increased ICP. Because of the potential danger of progressive hydrocephalus, surgical intervention should be planned in an urgent or semiurgent fashion. In those

cases in which obtundation or cardiorespiratory instability is present, immediate intervention with placement of an external ventricular drain is mandatory. In these cases, maximum care needs to be paid to avoid excessive drainage, which can result in upward herniation. The preoperative placement of an external ventricular drain in nonemergent cases is matter of surgeon preference, but in our practice we prefer to avoid it and to start dexamethasone (0.25 to 0.5 mg/kg per day), which usually relieves symptoms in 6 to 12 hours.

43.6.2 Surgical Approach

Positioning is dictated by tumor location and the patient's age. Usually, children younger than 2 years are placed prone with their head resting in a padded pediatric head holder. For older patients, rigid pin fixation is preferred, to increase stability and provide support for retracting devices.

For midline lesions, a vertical skin incision is performed from 1 cm above the external occipital protuberance to the upper cervical spine. An electric knife is then used to separate the posterior muscles of the neck. At this stage, to limit blood loss, care should be taken to cut through the ligamentous midline. Usually, the posterior arch of C1 is exposed but not removed. A suboccipital craniotomy is then performed, just below the transverse sinus and including the opening of the posterior rim of the foramen magnum. The dura is then opened in a Y pattern. It is important, at this stage, to be aware that, particularly in young children, the dura covering the posterior fossa is highly vascularized, so meticulous hemostasis is imperative. Depending on the size of the tumor, the mass effect exerted on the surrounding cerebellum may be substantial. In such cases, opening the cisterna magna is a useful strategy to drain some CSF and decrease ICP. Alternatively, for cystic tumors, a brain needle can be inserted through the dura into the cyst with subsequent aspiration of cyst fluid to achieve decompression.

For vermian lesions, the hemispheres are gently retracted bilaterally until the vermis is exposed and the tumor is visualized. Intraoperative ultrasound can aid in locating smaller tumors. A plane between PAs and surrounding cerebellum is usually well delineated. In order to delineate the anterior margin of the tumor, the fourth ventricle needs to be entered through the foramen of Magendie, so that, by insertion of a cottonoid, the floor of the fourth ventricle is protected during resection. The tumor is then resected piecemeal by aspiration and cautious coagulation. For large, solid lesions, an ultrasonic aspirator (e.g., Cavitron Ultrasonic Aspirator) can be employed. At the final stage, it is important to decide whether the cyst wall is neoplastic or reactive. To this end, when in doubt, multiple biopsies of the wall for frozen histology are recommended. It is preferable to leave the cyst wall in situ when it is not neoplastic.

For lesions located predominantly in the hemispheric region, a retrosigmoid approach may be considered. This has the advantage of sparing the midline structures of the cerebellum, thus preventing possible surgical complications, including cerebellar mutism.

For DFAs, the approach is the same, although the interface between normal tissue and tumor is less well defined. Surgical adjuvants, such as intraoperative frameless stereotaxy and intraoperative MR imaging, may provide useful guidance toward achieving the aim of a gross total resection (GTR).

In closure, the dura should be approximated in a watertight fashion, with the help, if needed, of an appropriate dural substitute. Dural closure is not essential but is advised to decrease the risks for chemical meningitis. Similarly, replacing the occipital bone is advised to decrease the risk for pseudomeningocele formation and to facilitate reoperation in case of tumor recurrence. Finally, it is imperative to meticulously approximate the muscle, fascia, and superficial layers to prevent CSF leakage and pseudomeningocele formation.

43.6.3 Surgical Complications

Postoperative mortality after posterior fossa tumor resection has been reported in the 1.5 to 5% range and is substantially decreased since the advent of modern microsurgical techniques.^{9, 11, 22} Common causes of mortality are surgical site hemorrhage, brain edema, and respiratory compromise secondary to brainstem violation.⁹ Common complications include CSF leakage, pseudomeningocele, meningitis (either infectious or aseptic), cranial nerve palsy, and ataxia.^{6, 10, 22} Cerebellar mutism is a unique consequence of posterior fossa surgery in children. Observed in 11 to 29% of patients, it is more commonly seen after the resection of vermian lesions, which explains why it is almost exclusively observed after medulloblastoma resection.⁶⁴ Brainstem involvement by the tumor may also be a significant risk factor for this complication.⁶⁵ Characteristically, it presents 1 to 6 days after an otherwise uneventful surgery with marked speech delay that is usually of limited duration (1 day to 4 months; average, 6 to 7 weeks). It can also be associated with ataxia, cranial nerve palsy, and emotional lability (the so-called posterior fossa syndrome). Recovery is spontaneous but frequently incomplete, as up to 68% of patients will have persistently impaired speech fluency and dysarthria 1 year after the resolution of mutism. Preoperative evidence of speech abnormalities has been found to be a positive predictor of postoperative mutism.⁶⁶ The pathophysiology of cerebellar mutism is unknown, but most authors agree that it derives from bilateral perturbation of the dentate–thalamocortical pathways with resulting interruption of excitatory stimuli from the cerebellum to supratentorial speech centers. The delayed onset has been explained as resulting from postsurgical hypoperfusion,⁶⁷ edema,⁶⁸ transient deregulation of neurotransmitter release,⁶⁹ or axonal injury caused by sudden release of the tumor mass effect.⁷⁰

43.6.4 Postoperative Management

Intraoperative MR imaging at the end of tumor resection may be used to verify the extent of resection. Otherwise, MR imaging of the brain with and without intravenous gadolinium injection should be obtained within 48 hours of surgery to assess the extent of resection. In this time window, the presence of enhancement is strongly suggestive of residual disease. Depending on the MR imaging findings, the decisional algorithm is as follows: If a GTR has been obtained, no other treatment is indicated, and only follow-up imaging is recommended. There is no consensus, however, on how long the follow-up should be; because recurrence in the setting of GTR is a rare event, some authors have recommended a short follow-up schedule, suggesting only a single imaging session 6 months postoperatively.⁷¹ Contrarily, because of the indolent nature of these tumors, 8 to

10 years has been considered a reasonable period of follow-up by neuroimaging,⁷² although most commonly recurrence or progression happens within the first 5 years after initial treatment.⁷³ If only subtotal resection has been achieved, early reoperation should be considered in cases in which it is deemed safe and feasible because of the survival advantage associated with GTR.⁷⁴

If nonresectable, residual low-grade tumor is present, expectant management with frequent imaging is currently employed at most centers. This is justified by the unpredictable behavior of residual tumors, which not infrequently have been shown to remain stable or even regress at long-term follow-up. In a series of 168 benign cerebellar astrocytomas, Pencolet et al found that 42% of patients who had incomplete resection experienced recurrence, versus 5.6% of patients with initial GTR.²² In another study, of 14 children with residual tumor, 5 had progression, 5 had tumor regression, and the remainder had stable disease at 5 years.⁷³ Gunny et al reported similar results, showing tumor regression in 45% of their patients during a follow-up period of longer than 6 years.⁷⁵

The majority of patients with cerebellar astrocytoma show resolution of the hydrocephalus after tumor resection, although up to 15% will need CSF diversion for progressive hydrocephalus.^{10,76} In comparison, almost half of patients with medulloblastoma require shunt placement.⁷⁶ Other than tumor histology, severe hydrocephalus, the presence of papilledema, and age younger than 2 years have been found to be significant predictors of shunt dependency.⁷⁷ In patients who meet one or more of these criteria, frequent radiologic and clinical assessment is recommended. Indications for CSF shunting include evidence of enlarging ventricles, progressive symptomatology, and persistent CSF leak. Children who receive preoperative ventricular drainage have an increased likelihood to remain shunt-dependent postoperatively.⁷⁸

43.6.5 Adjuvant Therapy

Patients whose tumor is completely resected do not need any further treatment. Chemotherapy and radiotherapy are usually considered in cases in which recurrence ensues or progression of residual disease is observed, if reoperation is not a possibility. Some authors have suggested that repeated resection should be attempted twice before radiotherapy is implemented in these patients.⁴ Others, particularly in light of recent results obtained with focal irradiation, suggest that noninvasive treatment should be favored to decrease surgical risks.

Upfront conventional radiotherapy to incompletely resected grade II gliomas failed to show any survival benefit compared with irradiation at tumor recurrence in a retrospective analysis of 90 patients younger than 20 years.⁷⁹ Also, although usually associated with an excellent tumor response rate, conventional radiation has not been demonstrated to prolong survival.^{73,80,81} For these reasons, the consensus has been to reserve irradiation for relapsing low-grade astrocytomas and for higher-grade astrocytomas and GBM.^{7,13}

More recent series describing results obtained with stereotactic radiosurgery have shown much more encouraging results; 50 patients with a diagnosis of PA who received stereotactic radiosurgery after partial resection or tumor recurrence had a 71% PFS at 5 years and 97.4% survival at 10 years. Small

(<8 cm³) size and solid rather than cystic tumor appeared to be the strongest variables for tumor response.⁸² In another study, 9 of 9 pediatric patients with residual cerebellar PA were progression-free at 5 years after treatment with conformal radiotherapy.⁸³ Finally, in a Phase II trial enrolling patients with low-grade astrocytomas treated with conformal radiotherapy, Merchant et al reported 5- and 10-year PFS rates of 87% and 74%, respectively, with a 10-year survival of 95%. Importantly, in the same series, the authors reported that cognitive impairment occurred only in children younger than 5 years. Other long-term side effects were hearing loss (4.9%), endocrinopathies, and vasculopathies (4.8%).⁸⁴

Chemotherapy remains the front-line adjuvant therapy in infants and young children to defer radiotherapy and its deleterious effect on brain development and cognition. The combination of vincristine and carboplatin demonstrated tumor reduction in 56% of low-grade astrocytomas and a PFS rate at 3 years of 68%.⁸⁵ Similarly, a tumor response in 70% of cases and a 3-year PFS rate of 78% was reported with a combination of cisplatin and etoposide.⁸⁶ For tumors progressing despite prior chemotherapy, temozolomide has been shown to be a promising option, resulting in a 54% response rate and a 49% PFS rate at 2 years.⁸⁷

43.7 Outcome

43.7.1 Prognostic Factors

The only two universally accepted and statistically validated factors associated with survival in patients with cerebellar astrocytomas are (1) low versus high grade and, in the case of low-grade tumors, (2) extent of tumor resection. Gender and age at diagnosis do not correlate with survival.⁷ There is still debate regarding whether low-grade diffuse astrocytomas are associated with worse outcome than PAs; Smoots et al found a statistically significant association of WHO grade II tumors with incidence of residual tumor in the brainstem and, consequently, with poor survival.⁸⁸ This was in agreement with other series, published by Sgouros et al⁸⁹ and Desai et al.¹¹ More recently, results from a series of 200 patients failed to show a significant prognostic value for tumor histology.⁹ Size of the tumor, midline location, and solid appearance have all been associated with worse functional outcome.⁹

43.7.2 Leptomeningeal Dissemination

Fifty-eight cases of disseminated PA have been reported in the literature. The primary tumor was located in the cerebellum in 33% of cases, whereas the majority of cases originated from optic-hypothalamic lesions. PFS rates at 5 years ranged from 50 to 60% with a combination of surgery, radiation therapy, and chemotherapy. Craniospinal irradiation does not seem to be superior to focal radiotherapy and chemotherapy for disease control.¹⁸

43.7.3 High-Grade Gliomas

Malignant cerebellar astrocytomas are rare. When they arise “de novo,” they more frequently affect children younger than

3 years.¹² Alternatively, they may result from malignant transformation of a prior low-grade tumor; malignant transformation of PA has been rarely reported, and in most such cases, it occurred after tumor irradiation.^{90,91} The time window between initial diagnosis and evidence of transformation ranged from 2 to 52 years.⁹⁰ There are 25 cases of primary cerebellar GBM reported in the literature and 8 secondary cases of GBM resulting from malignant transformation of lower-grade tumors,¹³ of which 2 were PAs.⁹⁰ Although symptoms at presentation are similar to those of lower-grade tumors, symptom progression is usually faster, and the diagnosis is made within a few weeks. A tendency for early leptomeningeal spread has also been reported.¹³ Despite aggressive surgical resection and adjuvant therapy, reported mean survival is 10 to 15 months.^{13,92}

43.8 Recurrence/Progression

After GTR, recurrence has been reported in 0 to 6% of patients with low-grade astrocytomas,^{22,71-73,93} with a mean interval of 59 months after surgery.⁷² Following incomplete resection, the rate of tumor progression reaches 50% of cases, and progression usually ensues in the first 3 to 4 years.^{72,73} In the majority of cases, recurrence is diagnosed radiologically rather than clinically, justifying the implementation of long-term radiologic follow-up for patients with incompletely resected tumors.⁹⁴ A recent series reported that 96% of the total recurrences/progressions happened within 8 years from initial surgery, and the authors concluded that radiologic follow-up should thus be extended to that interval.⁷² Although still debated, there does not seem to be a significant difference between recurrence or progression rates for PAs and for diffuse astrocytomas.^{72,94} In case of recurrence, reoperation is strongly recommended because it is associated with an excellent survival if GTR can be achieved^{7,93-95}). When GTR is not a feasible option, subtotal resection followed by adjuvant chemotherapy and/or radiotherapy/radiosurgery is appropriate.

43.9 Survival

Patients in whom complete tumor resection is achieved have an excellent prognosis, with 10-year survival rates ranging from 90 to 100%.^{7,72,89} On the other hand, subtotal resection is associated with a higher likelihood of tumor progression, resulting in 10-year survival rates as low as 50% in some series,^{89,96} although other authors report more favorable outcomes, with up to 85% patients alive at 10-year follow-up.⁷ The mean survival of patients with GBM is 10 to 15 months.¹³

43.10 Functional Outcome

Up to 60% of patients treated for cerebellar PA and followed for a period of 8 years showed permanent neurologic deficits, mainly disequilibrium, strabismus, and ataxia. Furthermore, behavioral disorders, such as irritability and tearfulness, were present in more than 50%.^{97,98} However, in the majority of cases, the deficits did not prevent independent functioning and a high school education.⁹⁷

43.11 Conclusion

Cerebellar astrocytomas are a heterogeneous group of tumors of childhood ranging from completely benign to extremely aggressive lesions. Low-grade tumors (WHO grades I and II) are the most frequent and are generally associated with a very good prognosis. Within this group, there is no agreement on whether PA carries a better prognosis than DFA, but evidence suggests that as long as complete resection is obtained, both have a very benign course, and cure can be very often achieved. The opposite is true for higher-grade tumors. To date, histology and extent of tumor resection are the only two validated predictors of PFS and overall survival; in light of this, the treatment plan for cerebellar tumors should always entail an aggressive approach aimed at complete resection (when this can be achieved with no or minor neurologic sequelae), and then further actions dictated by tumor grading and/or the presence of residual tumor. Patients with completely resected low-grade lesions should be followed by serial imaging. Second surgical resection should be considered for patients with residual tumor or recurrence. If this is not feasible, recent data support a role for stereotactic radiosurgery for local tumor control and extended PFS. Radiation is usually reserved for children older than 5 years of age to limit damage to the growing central nervous system. For younger children, chemotherapy is used. There are no indications to irradiate residual tumor before evidence of regrowth because spontaneous regression has been occasionally described. On the other hand, higher-grade tumors should receive maximum therapy, consisting of chemotherapy and irradiation following surgical resection.

Pearls

- Cerebellar astrocytomas are the second most common posterior fossa tumors in childhood, following only medulloblastomas.
- Histologically, the vast majority are PAs. There is no strong evidence suggesting that low-grade diffuse astrocytoma carries a worse prognosis than PA. High-grade tumors are rare.
- The extent of surgical resection and the histologic grade (low vs. high) are the only validated predictors of PFS and overall survival.
- If GTR is achieved, observation alone is recommended for low-grade tumors.
- If only partial resection of a low-grade tumor is achieved, the remnant should be carefully monitored with frequent neuroimaging.
- Upon recurrence, repeated resection to achieve a GTR is recommended if feasible. Otherwise, radiation therapy should be considered. In younger children, the use of chemotherapy should be implemented to postpone irradiation.

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44 Skull Base Tumors

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Pediatric skull base pathologies and their operative management pose unique challenges for the skull base surgeon. The entities in the differential diagnosis and the ages at presentation are diverse, and the skull base surgeon is faced with a heterogeneous patient population and a dynamic surgical anatomy characteristic of growing patients. Recent advances in imaging and treatments for skull base lesions require careful consideration when applied to the pediatric population. Indications for surgery have expanded to include both benign and malignant disease, and treatments and surgical approaches need to take into account treatment goals, potential long-term side effects of therapy, impact on craniofacial growth, cosmesis, postoperative care, and quality of life.

Pediatric skull base surgery encompasses a wide variety of surgical approaches, both open and endoscopic. There has been a dramatic increase in pediatric endoscopic approaches at our institution, which is a consequence of our experience in the adult population of patients requiring skull base surgery and an increased recognition of the benefits of endonasal surgery for the pediatric population. Decreased morbidity, faster postoperative recovery, and greater patient and family acceptance make endoscopic surgical approaches especially suitable for pediatric patients.

The primary aim of this chapter is to provide an overview of surgical approaches, both open and endoscopic, and their application to common pediatric skull base pathologies. Clinical examples of pathologies affecting different regions of the skull base are discussed, with particular reference to clinical evaluation, the relevant surgical anatomy and approaches, and reconstruction strategies. Specific planning and surgical considerations in the management of pediatric patients with skull base pathologies are highlighted.

44.1 Overview of Skull Base Anatomy

Successful cranial base surgery is based on an in-depth knowledge of the regional and embryologic anatomy of the developing skull base, an understanding of how specific pathologies affect the pediatric skull base, and an appreciation of the limitations and consequences of various surgical techniques in pediatric patients. Extensive training, complemented by dissection work in the laboratory, is crucial to achieve anatomical proficiency, a three-dimensional appreciation of the structural relationships, and a knowledge of anatomical variations. The skull base surgeon must master intracranial, extracranial, and endoscopic surgical anatomy.

The skull base can be considered in three different parts—anterior, middle, and posterior—with closely related intracranial and extracranial anatomical compartments (► Table 44.1). Detailed anatomy is beyond the scope of this chapter. Major considerations include a knowledge of (1) surgical anatomy for optimal access with minimum risk to critical neurovascular structures, (2) developmental anatomy of various growth

stages, (3) embryologic anatomy to understand surgical pathology, (4) vascular anatomy, and (5) reconstructive anatomy.

44.1.1 Anterior Skull Base

This portion of the skull base extends from the internal surface of the frontal bones anteriorly to the sphenoid ridge of the sphenoid bone posteriorly. The latter is joined medially by the chiasmatic groove (► Fig. 44.1). The intracranial surface is formed by the frontal, ethmoid, and sphenoid bones.¹ The frontal bones comprise the major part of the anterior cranial base, contributing to its lateral part. The orbital process of the frontal bone articulates posteriorly with the lesser wing of the sphenoid bone. Those two bones form the orbital roof and the optic canal, which transmit the optic nerve and ophthalmic artery. Posterolaterally, the optic canal is related to the anterior clinoid, and inferomedially to the posterior ethmoid sinus. The frontal sinus lies anteriorly between the external and internal walls (anterior and posterior tables) of the frontal bone.

The anterior cranial base faces the frontal lobes, with the rectus gyrus medially and the orbital gyri laterally. In the midline, the superior sagittal sinus continues to the floor of the anterior cranial base, where it connects with a small emissary vein at the foramen cecum. The fronto-orbital artery, a branch of the anterior cerebral artery, travels along the inferior and medial surface of the frontal lobe and is therefore at risk during anterior cranial base surgeries. The olfactory bulbs lie over the cribriform plates, and the olfactory tracts continue posterolaterally, closely applied to the surface of the brain as they pass over the optic nerves.

The midline of the anterior cranial base is related to the nasal cavity, ethmoid, and sphenoid sinuses. The ethmoid bone constitutes the anterior two-thirds of the midline anterior cranial base. The regions of the ethmoid bone related to the intracranial surface from medial to lateral are the crista galli, cribriform plate, and fovea ethmoidalis. The crista galli separates the anterior half of the cribriform plate in the midline and is attached to the falx cerebri. Anterior to the crista galli, the foramen cecum transmits an emissary vein responsible for the venous drainage from the nasal cavity to the superior sagittal sinus. In addition to the potential risk for the intracranial dissemination of nasal infections, lesions like nasal dermoid, glioma, and meningocele can communicate intracranially via the foramen.^{2,3} The thin lateral lamella of the cribriform plate continues laterally as the fovea ethmoidalis or roof of the ethmoid sinuses. The depth and angulation of the lateral lamella affect the risk for iatrogenic cerebrospinal fluid (CSF) leak during transethmoidal procedures. The olfactory filaments pass through the cribriform plate from the nasal cavity to the intracranial olfactory bulbs and are a route for the intracranial spread of sinonasal malignancy. The posterior third of the midline anterior cranial base is formed by the planum sphenoidale, which corresponds to the roof of the sphenoid sinus.

At the junction of the ethmoid sinus and orbit, the anterior and posterior ethmoidal foramina along the frontoethmoidal suture line transmit the anterior and posterior ethmoidal

Table 44.1 Anatomy

	Anterior skull base	Middle skull base	Posterior skull base
Intracranial structures	Anterior cranial fossa	Middle cranial fossa Pituitary fossa Cavernous sinus	Posterior cranial fossa
Osteology	Frontal bones Ethmoid bones Sphenoid bone—planum sphenoidale	Sphenoid bone Temporal bone	Sphenoid bone Occipital bone
Foramina	Foramen cecum Olfactory foramina Ethmoid foramina	Vidian canal Foramen rotundum Foramen ovale Foramen spinosum Foramen of Vesalius	Hypoglossal canal Foramen magnum
Extracranial structures	Frontal and ethmoid sinuses Nasal cavity Orbit Lacrimal apparatus	Sphenoid and maxillary sinuses Nasopharynx Fossa of Rosenmüller Pterygopalatine fossa Infratemporal fossa Parapharyngeal space Infrapetrous space	
Major vessels	Anterior and posterior ethmoid arteries Ophthalmic artery Fronto-orbital arteries Anterior cerebral arteries	Circle of Willis Internal carotid artery Superior and inferior hypophysial arteries Vidian artery Maxillary artery Sphenopalatine artery Posterior nasal artery Middle meningeal artery Accessory meningeal artery	Vertebral artery Basilar artery
Major nerves	Olfactory bulb Olfactory tract	Optic nerve Cavernous sinus nerves <ul style="list-style-type: none"> • Oculomotor nerve • Trochlear nerve • Abducens nerve • Trigeminal V₁ nerve (ophthalmic branch) • Trigeminal nerve Mandibular nerve Maxillary nerve Vidian nerve	Abducens nerve

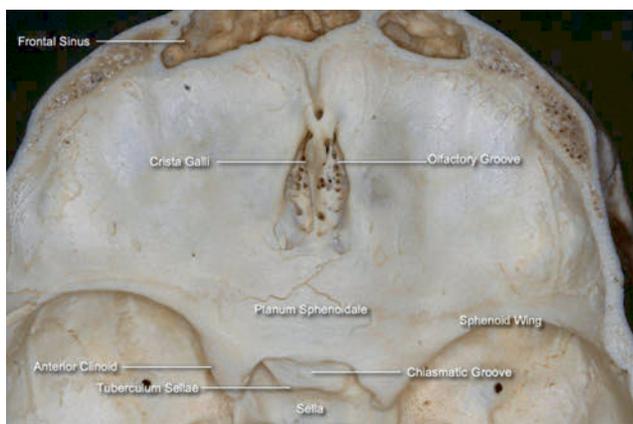


Fig. 44.1 Intracranial view of the anterior cranial base.

arteries, respectively (► Fig. 44.2). These arteries are derived from the ophthalmic artery within the orbit. From the orbit, the ethmoidal arteries enter the ethmoid sinuses via their respective foramina and run in a lateral-to-medial direction in the roof of the ethmoid sinuses. In some cases, they may lie below the ethmoid roof on a bony mesentery or pedicle and are at risk during endoscopic sinus surgery. The anterior ethmoidal artery is located between the second and third ground lamellae in a coronal plane tangential to the posterior surface of the globe. The posterior ethmoidal artery is often found at the junction of the fovea ethmoidalis and planum sphenoidale. These arteries diverge as they cross the roof of the ethmoid and need to be identified and ligated or coagulated during surgical procedures involving the anterior cranial base. Medially, the arteries enter the cranial cavity through the lateral lamella and re-enter the nasal cavity to supply the upper nasal septum.

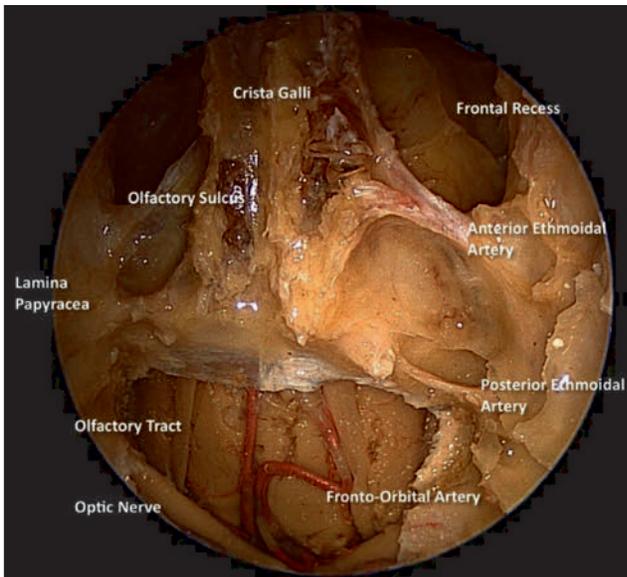


Fig. 44.2 Endonasal endoscopic view of the anterior cranial base demonstrating the relationship of the anterior and posterior ethmoid arteries to the orbit and the skull base.

44.1.2 Middle Cranial Base

The intracranial surface of the middle cranial base is formed by the sphenoid and temporal bones.¹ The limit between the anterior and the middle cranial bases is the sphenoid ridge joined medially by the chiasmatic groove. The transition between the middle and the posterior cranial bases is the petrous ridge joined medially by the dorsum sellae and the posterior clinoid process.¹

The intracranial surface of the middle cranial base can be divided into two regions: medial and lateral. The medial region is composed of the body of the sphenoid bone and is related to the pituitary gland and cavernous sinus, including the tuberculum sellae, pituitary fossa, middle and posterior clinoid processes, carotid sulcus, and dorsum sellae.¹ The greater wing of the sphenoid bone and the temporal bone (squamosal and petrosal segments) form the lateral portion of the middle cranial base, containing the middle cranial fossa. The optic strut runs under the optic nerve and separates it from the internal carotid artery (ICA). Pneumatization of the optic strut forms the lateral opticocarotid recess (OCR), observed endonasally in the sphenoid sinus (► Fig. 44.3).

The temporal bone has a pyramidal shape, the sides of which form the middle fossa floor (superior face), the anterior limit of the posterior fossa (posterior face), the muscle attachments of the neck and infratemporal fossa (anteroinferior face), and the muscular-cutaneous-covered side of the head (lateral), which forms the base of the pyramid. The temporal bone consists of four embryologically distinct components: the squamous, mastoid, petrous, and tympanic parts.

The area below the middle cranial fossa includes the infratemporal fossa, parapharyngeal space, infrapetrous space, and pterygopalatine fossa. The boundaries of the infratemporal fossa are the medial pterygoid muscle and the pterygoid process medially, the mandible laterally, the posterior wall of

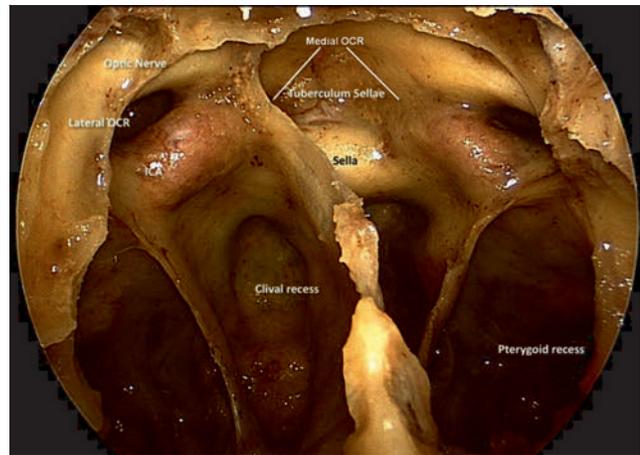


Fig. 44.3 Endoscopic view of the surface anatomy of the sphenoid sinus demonstrating the relationships of the optic canals, internal carotid arteries, and opticocarotid recesses. OCR, opticocarotid recess.

the maxillary sinus anteriorly, the greater wing of the sphenoid superiorly, and the medial pterygoid muscle joining the mandible and the pterygoid fascia posteriorly. The fossa opens into the neck below. The infratemporal fossa contains the branches of mandibular nerve, the maxillary artery, and the pterygoid muscles and venous plexus. The mandibular nerve exits the cranial base through the foramen ovale. The pterygoid venous plexus connects via the middle fossa foramina and inferior orbital fissure with the cavernous sinus and empties into the retromandibular and facial veins.¹ During a lateral infratemporal approach, the following structures form a linear plane superficial to the ICA canal: the lateral pterygoid plate, foramen ovale, foramen spinosum, and spine of the sphenoid. Deep to this linear plane, the eustachian tube overlies the petrous carotid canal.

The pterygopalatine fossa is located between the maxillary sinus anteriorly, the pterygoid process posteriorly, the palatine bone medially, and the body of the sphenoid bone above. The fossa communicates laterally via the pterygomaxillary fissure with the infratemporal fossa and medially through the sphenopalatine foramen with the nasal cavity. Both the foramen rotundum (with the maxillary nerve) and the pterygoid canal (with the vidian nerve) communicate with the pterygopalatine fossa via the posterior wall. The main contents of the fossa include branches of the maxillary nerve and vidian nerve, the pterygopalatine ganglion, and the pterygopalatine segment of the maxillary artery.

The parapharyngeal space is predominantly a fat-filled space but also contains the eustachian tube, pharyngeal branches of the ascending pharyngeal and facial arteries, and branches of the glossopharyngeal nerve. It is divided into two compartments, an anterolateral pre-styloid space and a posteromedial post-styloid space, by fascia from the styloid process to the tensor veli palatini muscle. The pre-styloid space contains the deep lobe of the parotid gland, minor salivary glands, a small branch of the mandibular nerve (cranial nerve V₃) to the tensor veli palatini muscle, the ascending pharyngeal artery, and the pharyngeal venous plexus, embedded in mostly fatty tissue. The post-styloid compartment

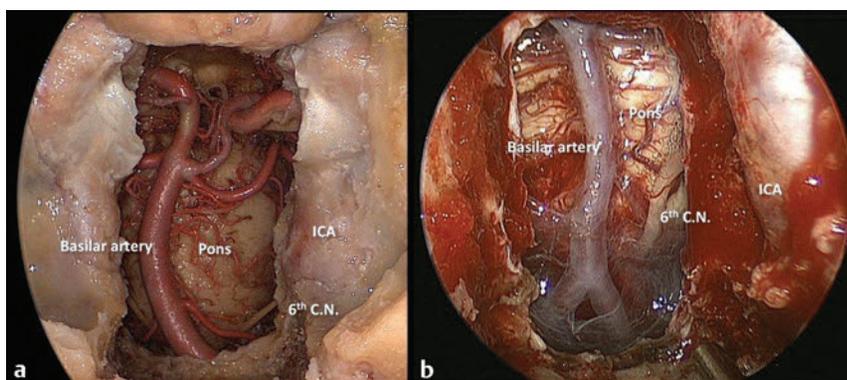


Fig. 44.4 (a) Cadaveric dissection demonstrating the course of cranial nerve VI. The nerve arises from the brainstem at the level of the vertebral-basilar junction. (b) Operative photo demonstrating the course of cranial nerve VI relative to the paraclival carotid artery. The nerve enters the Dorello canal at approximately the midpoint of the paraclival internal carotid artery. ICA, internal carotid artery; 6th C.N., sixth cranial nerve.

contains the ICA, internal jugular vein, cranial nerves IX through XII, the cervical sympathetic chain, lymph nodes, and glomus bodies.

Endonasally, the medial aspect of the middle fossa (Meckel cave) is lateral to the paraclival ICA and superior to the petrous segment of the ICA. The second division of the trigeminal nerve (foramen rotundum) and the vidian nerve (pterygoid canal) are helpful landmarks that define the area of the pterygoid and sphenoid just anterior to this. The Meckel cave is bounded by the lateral cavernous sinus superiorly containing cranial nerves III, IV, V₁, and VI. The foramen ovale is posterior to the lateral pterygoid plate, and the base of the pterygoid requires drilling to gain optimal access to this region.

44.1.3 Sphenoid Sinus

The surface anatomy of the sphenoid sinus is important for endonasal approaches to the pituitary and surrounding areas (► Fig. 44.3). The degree of sphenoid pneumatization and the patterns of septa vary greatly. Lateral septa almost always deviate toward the ICA, and care must be taken when they are removed. The sella is bounded by the clival recess inferiorly, cavernous sinus and ICA laterally, and optic canal superolaterally. The clival recess is bounded by the paraclival ICA and petrous apex laterally. The sixth cranial nerve courses superolaterally in the Dorello canal behind the paraclival ICA and is at risk for injury during drilling posterior to the paraclival ICA just below the level of the sellar floor (► Fig. 44.4).

44.1.4 Posterior Cranial Base and Craniocervical Junction

Surgical access to the posterior cranial fossa may be posterior, inferior, and medial to the temporal bone. The sigmoid sinus defines the posterior margin of the petrous temporal bone. The infrapetrosal space contains the jugular bulb and the lower portion of the inferior petrosal sinus; branches of the ascending pharyngeal artery; the glossopharyngeal, vagus, and accessory nerves; and the opening of the carotid canal through which the ICA enters the cranial base. Endonasally, the clivus lies anterior to the brainstem and can be divided into three segments: superior, middle, and inferior. The superior segment extends from the posterior clinoid to

Table 44.2 Flaps and their blood supply

Flap	Blood supply
Septal flap	Posterior septal artery
Pericranial flap, galeopericranial flap	Supraorbital and supratrochlear arteries
Temporoparietal flap	Superficial temporal artery
Temporalis muscle flap	Deep temporal arteries
Inferior and middle turbinate flaps	Branches of sphenopalatine artery
Palatal flap	Descending palatine artery

the sella floor and intracranially is related to the oculomotor nerve and posterior cerebral and superior cerebellar arteries. The middle segment extends from the sellar floor to the floor of sphenoid sinus and is related to the abducens nerve and the basilar and anterior inferior cerebellar arteries. The inferior segment extends from the floor of the sphenoid sinus to the foramen magnum and is related to the glossopharyngeal, vagus, and hypoglossal nerves and the vertebral-basilar junction. Inferolaterally, the hypoglossal foramen is bounded superiorly by the jugular tubercle and the occipital condyle inferiorly.

44.2 Reconstructive Anatomy: Pedicled Flaps

Major reconstructive options include the nasoseptal and scalp flaps. The latter encompass the pericranial, galeopericranial, temporoparietal, and temporalis muscle flaps. Another flap that may be used is the inferior turbinate flap. The middle turbinate and palatal flaps are generally not a practical option in the pediatric population. A summary of vascularized flaps and their blood supply is provided in ► Table 44.2.

44.2.1 Scalp

Understanding the layers of the scalp makes it possible to preserve function and plan reconstruction with pedicled scalp flaps. The scalp has five layers, designated by the acronym SCALP: skin, subcutaneous tissues, aponeurosis (galea),

loose areolar layer, and periosteum. The pericranial flap comprises the loose areolar layer and periosteum, whereas the galeopericranial flap includes the galeal layer. The pericranial flap is supplied by the supraorbital and supratrochlear vessels, which exit foramina or notches along the superior orbital rim. Laterally, the galea is continuous with the superficial temporal fascia. A temporoparietal flap, derived from this layer, receives its blood supply from the superficial temporal artery. The temporalis muscle, another important reconstructive flap, is covered by the deep temporal fascia. The deep temporal arteries, terminal branches of the internal maxillary artery, supply the muscle on its deep surface.

44.2.2 Nasoseptal Flap

The nasoseptal flap is pedicled on the posterior septal branches of the sphenopalatine artery, which run across the anterior surface of the sphenoid rostrum below the level of the sphenoid ostium and immediately above the choanal margin. The superior incision extends posteriorly from the level of the sphenoid ostium and is carried forward anteriorly along the nasal septum below the skull base. The inferior incision extends from the posterior choanal margin, curving medially along the posterior margin of the vomerine septum to the nasal floor, and is carried anteriorly along the junction of the nasal septum and nasal floor. The superior and inferior septal incisions are then joined with a vertical septal incision at the squamocolumnar junction. This mucoperichondrial, mucoperiosteal nasoseptal flap is then elevated off the cartilaginous and bony nasal septum. Further surgical details of the nasoseptal flap can be found elsewhere.⁴ This flap can be used to reconstruct defects of the anterior (cribriform plate, fovea ethmoidalis, planum), middle (sellar, lateral sphenoid recess), and posterior (clival, craniocervical junction) cranial base.

44.3 Vascular Anatomy

In many respects, the surgical approaches to the skull base and reconstruction with vascularized flaps are determined by the vascular anatomy. Detailed vascular anatomy allows the anticipation and avoidance of injury to critical vessels, including the ICA, basilar artery, circle of Willis, perforators, superior hypophysial, fronto-orbital, and ophthalmic arteries. It also allows the anticipation and ligation of critical vessels required to devascularize the surgical field, including the anterior and posterior ethmoid, sphenopalatine, and internal maxillary arteries.

The course of the ICA has particular relevance during approaches to the middle cranial fossa. The suprapetrous and infrapetrous approaches are defined as above and below the horizontal (petrous) segment of the ICA, respectively. At least five segments of the ICA have been described: parapharyngeal (extracranial), horizontal (petrous), paraclival, cavernous, and supraclinoid.⁵ Surgical landmarks are described in detail elsewhere.⁵ The ophthalmic artery branches off the ICA as it exits the cavernous sinus and runs inferomedial to the optic nerve. The circle of Willis comprises the ICAs, anterior cerebral arteries, anterior communicating artery, posterior cerebral arteries, and posterior communicating artery. A patent circle of

Willis is predictive of collateral cerebral blood flow, and anatomical variations are common.

44.4 Developmental Anatomy

Several important considerations include the development of certain pathologies, potential disruption of craniofacial growth with various surgical approaches (especially open) and anatomical limitations to surgical approaches in the growing pediatric patient. The latter is particularly important when considering transnasal approaches to the skull base, where development of the sinuses and configuration of the piriform aperture can limit access. Importantly, when considering transsphenoidal pituitary surgery, sphenoid sinus pneumatization can affect intercarotid distances and determine the amount of drilling to access the sellar. Furthermore, the development of the nasal septum relative to the cranium can limit the size of nasoseptal flaps for reconstruction.⁶

44.4.1 Skull Base and Facial Skeleton

There are three main components of the human skull: (1) the membranous neurocranium containing the flat bones of the skull, (2) the cartilaginous neurocranium forming the major part of the skull base, and (3) the viscerocranium or facial skeleton.⁷ The precursor of the cranial base is a cartilaginous plate, the chondrocranium, which subsequently undergoes endochondral ossification. The cranial base has two portions with distinct embryologic origins: the anterior part and the posterior part, derived from the neural crest and paraxial mesoderm, respectively. The anterior and posterior parts of the cranial base are separated by the sella turcica.

The anterior cranial base integrates with the mid and upper face to form a coordinated growth complex and serves as a template for facial growth. It carries the mid and upper face forward, inferiorly, and laterally. It grows at a faster rate than the posterior cranial base, and the growth occurs predominantly in the sphenothmoidal synchondrosis and in the cartilage between the ethmoid and frontal bones. From adolescence onward, progressive pneumatization of the frontal and ethmoid bones contributes to the rest of anterior cranial growth. Thus, anomalies of anterior cranial growth (including cretinism, Turner syndrome, and Down syndrome) and surgery of the anterior cranial base that disrupts critical growth centers affect both cranial and facial growth. In such cases, the craniofacial structure is characterized by a short, retrognathic face due to reduced length of the cranial base and increased angulation between the anterior and posterior cranial base.

In contrast, the mandible articulates with the posterior cranial base, and variation of the growth and orientation of the cranial base can affect jaw position and occlusion. Mandibular prognathism has been attributed to abnormalities of posterior cranial base growth.

Skeletal maturation of the skull shape begins with the midline cranial base (7.7 years), followed by the lateral skull base (11.7 years), and finally the face (15.7 years).⁸ Hence, a definitive adult shape of the basicranium is obtained at approximately 12 years. The maturation of craniofacial size follows a superior–inferior gradient, beginning at the neurocranial outline in the midline (11.4 years), followed by the midline cranial base (13.6 years) and the lateral cranial floor and face (15.7 years).

During development of the primitive frontal nasofrontal process (the anterior neuropore), two openings become apparent. The fonticulus frontalis appears between the frontal and nasal bones, while the foramen cecum appears as a midline opening anterior to the crista galli. A diverticulum of dura projects through the fonticulus frontalis or through foramen cecum into the prenasal space, which is found inferior and posterior to the frontal and nasal bones but superior and anterior to the septal cartilage. The dura temporarily approximates the skin and subcutaneous tissues of the midnasal bridge at the osseous cartilaginous junction. Failure of the involution of this diverticulum can lead to the development of nasal dermoid sinus cysts, nasal gliomas, and meningoencephaloceles. All of these lesions have in common certain elements of disjunction or failed primary neurulation of the anterior neuropore. Craniofacial malformations have been reported to varying degrees in all three conditions, and magnetic resonance (MR) imaging is the imaging modality of choice for all these lesions.

44.4.2 Sella and Pituitary Gland

The pituitary gland is ectodermal in origin and has dual embryologic development. The anterior and intermediate lobes develop from oral ectodermal elements derived from the Rathke pouch, and the posterior lobe develops from neural ectoderm. An invagination (Rathke pouch) forms from the primitive stomodeum, cranial to the buccopharyngeal membrane, and extends toward the invagination derived from the neuroectoderm (infundibulum). The anterior portion of the Rathke pouch epithelium proliferates to form cells of the adenohypophysis, while the posterior portion remains largely as a cleft (intermediate lobe) between the anterior and posterior (neurohypophysis) lobes.

Neoplasms arising from the anterior lobe are classic pituitary adenomas, and their phenotype depends on the proliferating cell type. An accumulation of epithelial secretions from the intermediate lobe is thought to underlie the pathophysiology of Rathke cleft cysts. Although still debatable, the general consensus is that craniopharyngioma arises from the neoplastic transformation of cells in the Rathke cleft. Given the close relationship between the cells of origin of these pathologies, adenomas may occur simultaneously with Rathke cleft cyst.⁹

44.4.3 Frontal, Ethmoid, and Maxillary Sinuses

The paranasal sinuses develop at different stages, which is important to keep in mind, especially when endonasal (transnasal, transsinus) approaches to the skull base are being considered. The ethmoid and maxillary sinuses are present at birth and are well developed by 3 years of age. The frontal sinus develops at approximately 7 years of age and becomes fully pneumatized by 12 years.

44.4.4 Sphenoid Sinus

Sphenoid sinus pneumatization begins after age 2 at the anteroinferior wall of the sphenoid bone. A recent study showed that by 6 to 7 years of age, the sphenoid anterior wall is fully pneumatized in all patients, and 88% of the planum is pneumatized.^{10,11} The sella turcica and middle cranial fossa portion of the sphenoid bone in 6- to 7-year-old patients on average had 77% of the anterior sellar wall and 32% of the sellar floor pneumatized. There was no dorsum pneumatization in 84% of patients younger than 16 years, and the sellar floor length in patients younger than 2 years was 66% of that in adults. Pneumatization in the superior clivus and posterior cranial fossa aspect begins after the age of 10 years.

The intercarotid distance at the level of the cavernous sinus is significantly narrower in patients up to 6 to 7 years old than it is in adults, whereas there is no significant difference in patients 9 to 10 years and older.^{10,11} At the level of the superior clivus, the distances are similar in pediatric and adult patients.

Although incomplete sphenoid sinus pneumatization necessitates more drilling, the early maturation of the intercarotid distances and the use of intraoperative imaging are not a contraindication to endonasal approaches to the sella in pediatric patients. It is also important to consider the age-specific length of the pituitary fossa, which increases by more than 50% from age 2 to adulthood.

44.5 Pediatric Skull Base Tumors

A wide variety of skull base pathologies can affect pediatric patients (► Table 44.3). Tumors and other lesions may arise within the skull base, traverse the cranial base with either intracranial or extracranial origins, or present in single or multiple sites.

Table 44.3 Skull base pathology

Anterior cranial base, nasal cavity, maxillary sinus, orbit	Middle cranial base, sphenoid, sella, infratemporal fossa	Posterior cranial base
Meningoencephalocele	Meningoencephalocele	Chordoma
Nasal dermoid	Pituitary adenoma	Vestibular schwannoma
Glioma	Craniopharyngioma	Epidermoid cyst
Mucocele	Cholesterol granuloma	Glomus jugulare
Juvenile angiofibroma	Trigeminal schwannoma	Osteomyelitis
Fibrous dysplasia	Angiofibroma	
Fibro-osseous tumors	Sarcomas	
Esthesioneuroblastoma		

The latter is characteristic of hereditary tumors, metastatic deposits, and developmental anomalies. These pathologies can involve the anterior, middle, and posterior skull base and the corresponding intracranial fossae and extracranial regions, which include the nasal cavity, paranasal sinuses, orbits, pterygopalatine and infratemporal fossae, pharynx, and parapharyngeal and craniocervical regions. The differential diagnosis depends on age, sex, associated developmental anomalies, location, and clinical and imaging characteristics.

44.5.1 Clinical Presentation and Differential Diagnosis

The clinical presentation is influenced by the age at presentation and by the nature and site of the lesion. The term *congenital* refers to a presentation at or within 1 month of birth and does not indicate the pathophysiology. Often, congenital lesions consist of developmental anomalies; however, hamartomas, choristomas, and teratomas may also present congenitally. The symptomatology is diverse, and in-depth knowledge of the anatomy and cranial nerve physiology is imperative for a correct clinical topographic diagnosis. An adequate clinical examination can indicate the location and estimate tumor extent. However, this may not always be possible in the very young. Endocrine symptoms such as failure to thrive, short stature, and lack of sexual development often predominate in children with pituitary pathologies. Furthermore, nonspecific symptoms, including headache, weight loss, vomiting, weakness, and loss of appetite, may also occur. Symptoms characteristic of lesions involving the anterior, middle, and posterior skull base are summarized in ► Table 44.4.

The physical examination should include a complete assessment of cranial nerve function. In patients with nasal congestion, rhinorrhea, or airway obstruction, an evaluation by otolaryngology should be performed and should include nasal endoscopy. In patients with olfactory dysfunction, objective documentation can be performed. Visual symptoms should be evaluated further by an ophthalmologist and may include visual field testing in addition to a routine examination. Symptoms of hearing loss or vestibular dysfunction can be evaluated further with audiometric testing and vestibular tests if necessary. Lower cranial nerve dysfunction may require an evaluation of swallowing function and aspiration

risk with a functional endoscopic examination of swallowing (FEES) examination or radiography (barium esophagogram). If CSF rhinorrhea is suspected, provocative tests including a Valsalva maneuver can be performed. Testing of collected fluid for β_2 -transferrin or beta trace protein will confirm the presence of CSF.

44.5.2 Imaging in Skull Base Surgery

Computed tomography (CT) and MR imaging provide complementary information regarding the bone and soft-tissue anatomy, respectively, for diagnosis, preoperative planning, the intraoperative period, and postoperative surveillance. Bone erosion, defects, remodeling, hyperostosis, and calcification are well recognized on CT scans. CT angiography is especially helpful to evaluate the vasculature within and surrounding a tumor and is preferred for intraoperative navigation. MR imaging is superior for delineating intracranial or intraorbital invasion and determining the nature of the lesion. Fluid collections (meningocele, obstructed sinus) appear bright on T2-weighted sequences, although chronic sinus obstruction with a high protein content may appear dark on both T1 and T2 sequences. Fat appears bright on T1 and dark on T2 images, which explains the MR imaging appearance of lesions with a high lipid content, such as cholesterol granulomas. Chondromatous neoplasms (clival chordomas, chondrosarcomas) characteristically enhance on T1-weighted MR images with contrast and exhibit a high signal on T2-weighted sequences. Special sequences, such as diffusion-weighted imaging (DWI), are helpful in confirming an epidermoid tumor.

The vascularity of tumors is demonstrated by tumor enhancement on CT with contrast and flow voids on MR imaging. Nasopharyngeal angiofibromas classically enlarge the pterygopalatine fossa and appear as an enhancing lesion with contrast on both MR imaging and CT. Angiography is used to confirm the diagnosis of highly vascular tumors (angiofibroma, paraganglioma) and for the preoperative embolization of feeding vessels.

Preoperative imaging (CT angiography and MR imaging) also provides information regarding the intracranial circulation and collateral cerebral blood flow (patency of the circle of Willis). If sacrifice of the ICA or another major vessel is anticipated or planned, a preoperative balloon test occlusion with neuromonitoring is performed. Additional measures of cerebral blood flow,

Table 44.4 Signs and symptoms

Anterior skull base	Middle skull base	Posterior skull base
Olfactory dysfunction <ul style="list-style-type: none"> • Quantitative (hyposmia, anosmia, hyperosmia) • Qualitative (dysosmia) Proptosis Epiphora Nasal obstruction Epistaxis Facial deformity Diplopia Blurred vision Facial numbness Sinusitis Personality changes	Pituitary dysfunction Visual field loss Trigeminal neuralgia or numbness Facial palsy Ptosis Diplopia Trismus Eustachian tube dysfunction Temporal bone involvement (hearing loss, tinnitus, vertigo)	Tinnitus Hearing loss Balance problems Swallowing difficulties Hoarseness Speech problems Dysarthria Shoulder weakness Various syndromes

including perfusion CT and perfusion MR imaging, provide further objective assessment.

Positron emission tomography (PET) shows cellular activity in the body, primarily through the detection of labeled glucose taken up by the tissues under examination. This may be combined with CT (PET-CT) to give a better anatomical definition. Although this technique eventually may be useful for the identification of primary tumors, it is most appropriate for the detection of metastasis and local recurrence of high-grade malignancies.

44.5.3 Operative Management

The choice of a surgical approach depends on the diagnosis, surgical goals, surgical access, reconstructive options, patient comorbidities, experience of the surgical team, potential complications, and available resources. Goals for surgery are outlined in the box “Surgical Goals in the Pediatric Patient (p.294).” The optimal approach is one that provides adequate access and superior visualization and minimizes potential morbidity, especially that associated with manipulation of the neural and vascular structures, including retraction of the brain.

Surgical Goals in the Pediatric Patient

- Diagnostic biopsy
- Curative surgery
- Palliation, including pain management
- Salvage surgery, including after radiotherapy, chemotherapy, and chemoradiotherapy
- Tumor debulking, for decompression before chemoradiotherapy

Skull base surgery is team surgery and requires the close coordination of team members. Both CT and MR imaging are used for intraoperative navigation, which aids anatomical localization during the surgery, including identification of important neural and vascular structures, determination of tumor margins, and assessment of the extent of resection. Intraoperative imaging (intraoperative CT or MR imaging) is sometimes performed to assess the extent of tumor resection, detect complications (including hemorrhage), or visualize residual tumor by updating the navigation scan following the shift associated with tumor resection.

Neurophysiologic monitoring of cortical function with somatosensory evoked potentials (SSEPs) provides an overall assessment of cerebral perfusion, which can be adversely affected by hypotension or subdural collections (air or fluid).¹² Brainstem evoked response is used to monitor brainstem function during surgeries of the posterior fossa and electromyography to monitor the motor function of cranial nerves.

44.5.4 Surgical Approaches

Approaches to the Anterior Cranial Base

Surgical approaches to the cranial base can be classified based on the anatomical region (► Table 44.5). External approaches are classified by cranial fossa, whereas endonasal approaches are classified as surgical modules in the sagittal and coronal planes. In open approaches, craniofacial osteotomies provide access to the cranial base and help minimize brain retraction.

Anterior Cranial Base: Craniofacial Resection

Historically, the craniofacial approach pioneered by Ketcham and others has been the standard surgical option for the treatment of anterior cranial base pathology. This consists of a transcranial approach combined with a transfacial approach. A bicoronal incision is made over the vertex of the scalp from ear to ear. Laterally, the incision may be extended inferiorly in the preauricular skin crease to increase exposure. The posterior scalp flap can be elevated in a subgaleal plane to expose extra pericranium if needed for reconstruction. The anterior scalp is elevated from the underlying cranium with separation of the periosteum from the deep temporal fascia of the temporalis muscle at its margin. Laterally, the superficial layer of the deep temporal fascia is incised several centimeters above the zygomatic arch, and the interfascial fat pad is elevated with the scalp to avoid injury to the temporal branches of the facial nerve.

At the level of the superior orbital rims, the supratrochlear and supraorbital neurovascular bundles are carefully dissected free from their respective foramina to preserve the blood supply of a pericranial flap; small osteotomies may be necessary if the foramina are complete. Periosteum is elevated from the orbital roofs, glabella, and nasal bones, and the scalp is retracted inferiorly.

A bifrontal craniotomy is performed that encompasses the anterior and posterior tables of the frontal sinus. In the traditional anterior craniofacial resection craniotomy, the inferior osteotomy is placed just above the prominence of the brow. To minimize brain retraction, the supraorbital bar, including the superior orbital rims and glabella, can be removed in a single unit (subfrontal approach). Removal of the supraorbital bar requires elevation of the frontal dura from the orbital roofs. A reciprocating saw is used to transect the orbital rims at the lateral margin of the craniotomy. The orbital contents are protected while the orbital roof is transected with a drill and the bone is drilled anterior to the crista galli. For the subfrontal approach, a final transverse bone cut at the nasion transects the frontal recess and frees the bone segment.

The dura is separated from the crista galli and incised anteriorly to the cribriform plate and laterally along the medial margin

Table 44.5 Summary of surgical approaches to the cranial base

Approach type	Anterior cranial base	Middle cranial base	Posterior cranial base
Open	Craniofacial resection Subfrontal or subcranial craniotomy	Lateral infratemporal skull base approach	Retrosigmoid craniotomy Far lateral cervical approach
Endoscopic	Endonasal resection of anterior cranial base Endonasal transplanum, transcribriform approach	Endonasal suprapetrous approach	Endonasal transclival and transodontoid approach Endonasal infrapetrous approach

of the orbit. The olfactory bulbs and tracts are dissected free from the frontal lobes, and the olfactory tracts and dura are incised posteriorly over the planum. The bone margins are then drilled to communicate with the sinuses, staying anterior to the optic canals.

Frequently, the craniofacial resection combines transfacial approaches with the bifrontal craniotomy. The aim of the transfacial approaches is to provide an adequate field for the dissection and resection of the lesion from the nasal cavity, paranasal sinuses, and orbit. Options include a lateral rhinotomy, midfacial degloving, and an endoscopic endonasal approach. In a lateral rhinotomy, a skin incision is started at the midpoint between the nasal dorsum and the medial canthus. The incision respects facial subunits and extends along the lateral surface of the nose to the nasal alar, then curves around the nostril to the nasal sill.^{13,14} The incision communicates with the nasal cavity along the piriform aperture. Additional exposure can be obtained by extending the incision with a subciliary or transconjunctival incision superiorly (Weber-Ferguson incision), or by incising the upper lip along the lateral philtrum. After exposure of the facial skeleton through these incisions, osteotomies are performed according to the location and size of the tumor. In most situations, except when subcutaneous tissue and skin are involved, in which case skin incision is required, the exposure afforded by these transfacial incisions can be easily obtained by other means (midfacial degloving or endoscopic endonasal approaches). Thus, lateral rhinotomy is rarely used.

The midfacial degloving approach avoids a facial incision and provides better bilateral exposure. A mucosal incision is made in the gingivolabial sulcus, and periosteum is elevated from the anterior maxilla. The incision communicates with the nasal cavity along the piriform aperture, and the nasal soft tissues are elevated from the anterior edge of the nasal septum following a full transfixion incision. Bilateral transmaxillary antrostomies and medial maxillectomies provide additional exposure. The midfacial degloving approach may be supplemented with endoscopy to provide better visualization.

After the appropriate transfacial or endoscopic approach, the tumor is removed en bloc, if possible, by dissecting around the periphery of the neoplasm with opening of the sinuses and transection of the nasal septum. The cranial base specimen is then mobilized through the bone cuts in the cranial base and delivered transcranially.

Reconstruction of the resultant defect is necessary to provide separation of the cranial and nasal cavities and prevent CSF leak, meningitis, and pneumocephalus. The dural defect is repaired primarily. Suitable materials include synthetic dural substitutes, fascia lata, temporalis fascia, pericranial graft, and cadaveric pericardium. An inferiorly based pericranial flap is then reflected posteriorly to cover the entire defect in the anterior cranial base. Rigid reconstruction with a bone graft or alloplastic material is not necessary. It is important to place the flap inferior to the replaced supraorbital bar, with a small gap left to prevent compression of the vascular pedicle.

Anterior Cranial Base: Endoscopic Endonasal Resection

Endoscopic endonasal techniques can be used for the resection of sinonasal malignancies. The intranasal portion of the tumor

is first debulked to provide visualization of the margins and assess the extent of the tumor. Uninvolved sinuses are opened to allow visualization of the medial orbits, nasofrontal recesses, and sphenoid sinus. Bony landmarks (optic canals, carotid canals) are identified and the margins of resection are defined. In most cases, this includes the posterior wall of the frontal sinus, the medial walls of the orbit, the roof of the sphenoid sinus, and the nasal septum. The nasal septum is transected inferior to the area of tumor involvement from the frontal sinus to the rostrum of the sphenoid bone. Margins from the nasal septum mucosa are sent for frozen section analysis. If the septal mucosa is not involved by the tumor, a septal flap can be harvested for later reconstruction.

After harvesting of the septal flap, bilateral frontal sinusotomies are performed with removal of the floor bilaterally (Draf III procedure). The bone of the medial orbit is removed on the side of greatest tumor involvement. The tumor is devascularized by sacrifice of the anterior and posterior ethmoid arteries bilaterally. The arteries are identified at the junction of the orbit and skull base and are cauterized with bipolar electrocautery or ligated with hemoclips.

The bone of the anterior cranial base is thinned with a drill to facilitate the elevation and removal of bone, allowing full exposure of the dura and the area of dural invasion. Bone removal extends from the crista galli to the planum sphenoidale and to the medial orbits bilaterally. The dura is then cauterized and incised lateral to the tumor. Cortical blood vessels are identified and carefully freed from the dura. The falx is cauterized and transected anteriorly to allow mobilization of the dural specimen. The olfactory bulbs are dissected from the surface of the brain and remain attached to the dural specimen. If there is a focal area of brain invasion, the surrounding cortical tissue is removed by careful and limited suction dissection to achieve clear margins. The olfactory nerves are then transected posteriorly, and the final posterior dural incision is made to free the specimen. Additional dural margins may be excised for frozen section analysis before reconstruction.

After complete resection of the anterior cranial base, an inlay collagen or fascial graft is placed and the septal flap is positioned to cover the defect. If a septal flap is not available because of tumor involvement or insufficient dimension, a modified version of the extracranial pericranial flap is used.¹⁵ A bicoronal scalp incision is made, and the scalp is elevated to the level of the nasal bones. The bone at the level of the nasion is removed with a drill to create a window large enough to transmit the pericranial flap (approximately 1 × 2 cm). The flap is then transposed through the defect inferior to the frontal sinusotomy and positioned over the dural defect, with a drainage pathway for the frontal sinuses maintained on one side.

Approaches to the Middle Cranial Base

Open Approach: Lateral Infratemporal Skull Base Approach

The middle cranial fossa is typically accessed with a lateral transcranial approach. A bicoronal scalp incision is extended laterally in a preauricular skin crease to the inferior margin of the tragus. If transcervical exposure is required, it may be continued into the neck (parotidectomy incision). The scalp is

elevated superficial to the deep temporal fascia to the level of the zygomatic arch.

The lateral approaches to the middle cranial base include the transpterosal approaches, preauricular infratemporal approach, and frontotemporal approach. The frontotemporal (pterional) craniotomy serves as the standard approach to the middle cranial fossa. This approach can be extended with orbitozygomatic osteotomies, depending on the location of the lesion. Orbitozygomatic osteotomies incorporate the superior and lateral parts of the orbit and the zygoma to the standard pterional bone flap, enhancing the low exposure and improving access to the anterior cranial base and parasellar region. Osteotomies are placed across the superior orbital rim, body of the zygoma, and posterior attachment of the zygomatic arch. If exposure of the petrous ICA is necessary, the glenoid fossa can be included with the bone segment. With retraction of the temporalis muscle, a subtemporal craniectomy provides access to the foramen ovale, eustachian tube, and petrous segment of the ICA. This approach also can reach the sphenoid sinus, infratemporal fossa, and pterygopalatine fossa. Bony reconstruction consists of plating of the bone segments and augmentation with titanium mesh. The temporalis muscle covers the craniotomy site, and if dura or petrous ICA is exposed, temporalis muscle can be transposed to protect these tissues.¹⁶

Endoscopic Endonasal Approach: Middle Cranial Base

The endoscopic endonasal approaches permit access to different areas of the middle cranial base: the sella turcica, cavernous sinus, Meckel cave, petrous apex, and infratemporal fossa. Wide exposure of the sphenoid sinus is a common step in each endoscopic endonasal approach to the middle cranial base. Key anatomical structures (optic nerves, internal carotid arteries, cranial nerve V₂, and vidian nerve) are identified within the sphenoid sinus and then followed to other areas of the skull base.

Independently of the area approached in the middle cranial base, the endoscopic endonasal exposure is initiated by lateralization of the inferior and middle turbinates to increase the space for the insertion and manipulation of instruments. The right middle turbinate may be resected to improve visualization of the surgical field. The contralateral middle turbinate is lateralized and the nasoseptal flap is harvested for reconstruction of the cranial base defect at the end of the procedure. The flap can be stored in the nasopharynx or in the ipsilateral maxillary sinus during the operation. A partial posterior nasal septectomy in addition to wide bilateral sphenoidotomies and posterior ethmoidectomies completes the nasal corridor. This corridor provides access to the sellar region and to the cavernous sinus.

The corridor can be expanded laterally by adding a transpterygoid approach to reach the lateral recess of the sphenoid sinus, Meckel cave, and petrous apex. The transpterygoid approach begins with opening of the maxillary sinus and removal of the orbital process of the palatine bone and posterior wall of the maxillary sinus, exposing the pterygopalatine fossa periosteum. Terminal branches of the internal maxillary artery (sphenopalatine, posterior septal, palatovaginal, vidian, and descending palatine arteries) are sacrificed, and the pterygopalatine contents are lateralized to expose the base of the pterygoid plates and the vidian artery in the vidian (pterygoid) canal. The

descending palatine artery and the greater palatine nerve are preserved in the greater palatine canal at the inferomedial margin of the dissection. Once the vidian canal is identified, drilling can then proceed along its inferior and medial aspect. The vidian nerve dissection orients the surgeon toward the lateral portion of the foramen lacerum and the most superficial portion of the petrous ICA.

The transpterygoid approach can be extended to the pterygoid plates. In such cases, the corridor created provides access to the eustachian tube and the infrapetrous region. The infratemporal fossa is approached by removing the posterior wall of the maxillary sinus. This approach provides access to the pterygoid venous plexus, masticator muscles, and cranial nerve V₃ branches.

Approaches to the Posterior Cranial Base

Open Approach: Retrosigmoid Craniotomy

A postauricular incision is made and a subperiosteal flap is elevated. The incision may be extended anteriorly into the upper cervical region for control of the proximal ICA, isolation of the lower cranial nerves, and exposure of the condyle. The upper cervical musculature (sternocleidomastoid and trapezius muscles) is detached from the mastoid and suboccipital region, and a craniotomy is performed posterior to the mastoid and sigmoid sinus. A mastoidectomy with removal of the tip provides greater access to the jugular bulb and foramen.

If a large tumor involves the temporal bone and complete access to the extracranial ICA is needed, a Fisch type C approach provides wide exposure of the middle and posterior cranial fossae. The incision extends from the temporal area to the upper cervical region. A conchal bowl incision through the skin and cartilage allows elevation of the auricle with the skin flap; the stump of the external auditory canal remains. The facial nerve can be transposed for additional exposure or remain in situ. A transtemporal approach is then performed with dissection of the ICA to the carotid canal.

The surgical defect can be reconstructed with temporalis muscle transposition or a posteriorly based pericranial flap (occipital artery). The craniotomy site is covered with titanium mesh or a plate, and the cervical musculature is reattached.

Endonasal Transclival and Transodontoid Approach

The endonasal approach provides optimal access to the clival region from the posterior clinoids to the foramen magnum. A sphenoidotomy is performed, and the mucosa of the nasopharynx and underlying musculature is resected from the floor of the sphenoid to the ring of the C1 vertebra and between the nasopharyngeal eustachian tube orifices. It is important to localize the parapharyngeal ICA with image guidance to avoid injury with dissection or electrocautery. The clivus may be anatomically considered in thirds. The upper third includes the posterior clinoids to the sella floor. Exposure of the posterior clinoids often requires pituitary gland transposition for intradural dissection. The sella is opened widely, and the lateral attachments of the pituitary gland are lysed with possible sacrifice of the inferior hypophysial arteries on one or both sides. If the posterior planum is removed, the gland can be displaced into

the suprasellar space with preservation of the pituitary stalk and the superior hypophysial vessels. The middle clivus extends from the floor of the sella to the floor of the sphenoid sinus. Bone in this area is bounded by the parapharyngeal ICAs, and during drilling the sixth cranial nerve is susceptible to injury posterolateral to the vessels in the Dorello canal.¹⁷ The inferior clivus extends to the foramen magnum. Intense venous bleeding from the clival plexus is often encountered and can be controlled with application of the hemostatic materials of choice, including Surgifoam (Johnson & Johnson, New Brunswick, NJ) and FloSeal (Baxter, Deerfield, IL). The sixth cranial nerve exits the brainstem at the level of the vertebralbasilar junction and is susceptible to injury with opening of the dura (► Fig. 44.4).

If exposure of the upper cervical spine is necessary (basilar invagination, foramen magnum tumor), the anterior ring of C1 is exposed and removed. The odontoid and upper body of C2 can be drilled, and the ligamentous attachments are resected. Laterally, dissection is limited by the vertebral arteries.

Partial-thickness dural defects posterior to the clivus can be simply covered with fibrin glue. Septal mucosal flaps are usually inadequate in size, and reach for large and deep clival or odontoid dural defects and supplementation with fat grafts may be necessary. Pericranial flaps can be used to cover these defects if a vascularized flap is needed.

Endonasal Infrapetrous Approach

The infrapetrous approach is defined by the course of the petrous and parapharyngeal ICA. A lower transclival approach is combined with a transpterygoid approach, and the location of the petrous ICA is defined by using the vidian nerve as a landmark. Bone inferomedial to the pterygoid canal is carefully drilled, and the dense fibrocartilage of the foramen lacerum is exposed. The medial eustachian tube is resected, and the fibrocartilage is transected inferior to the foramen lacerum. This provides access to the inferior aspect of the petrous bone. Lateral dissection is limited by cranial nerve V₃ and the parapharyngeal ICA.

At the level of the foramen magnum, removal of bone laterally exposes the hypoglossal canal and nerve. The bone superior to the hypoglossal nerve is the jugular tubercle and is bounded laterally by the jugular bulb. The occipital condyle is inferior to the hypoglossal nerve; excessive removal of this bone on both sides can destabilize the craniocervical junction.¹⁸

Endoscopic Endonasal Approaches in the Pediatric Population

Specific Considerations

With improvements in instrumentation and the training of skull base teams, the endoscopic endonasal approach to pediatric sinonasal and skull base lesions has become a reality^{19–21} (► Table 44.6). Although the principles of surgery are the same for adult and pediatric patients, pediatric patients may present unique challenges based on the indications for surgery, anatomical access, and skull base reconstruction. It is important to have a skull base team with adequate expertise and experience. This may include both adult and pediatric otolaryngologists and neurosurgeons.

Table 44.6 Lesions treated endoscopically reported in the literature

Disease classification	Pathology
Nonneoplastic	Choanal atresia Rathke cleft cyst Encephalocele Meningocele Cerebrospinal fluid leak Arteriovenous fistula Aneurysmal bone cyst
Neoplasm, benign	Pituitary adenoma Juvenile nasopharyngeal angiofibroma Glioma Epidermoid Olfactory groove schwannoma Teratoma Neurofibroma Ossifying fibroma Osteoma Langerhans cell histiocytosis Hemangioma Leiomyoma
Neoplasm, malignant	Chordoma Craniopharyngioma Germinoma Neuroendocrine tumor Rhabdomyosarcoma Lymphoma

Indications

Applications of endonasal approaches in the pediatric population include biopsy for diagnosis, definitive treatment of benign neoplasms (including pituitary adenoma, angiofibroma, and craniopharyngioma), and downstaging of high-grade malignancies, such as rhabdomyosarcoma. The lesser morbidity and greater acceptance of an endonasal approach lower the threshold for surgical biopsy and provide greater flexibility for the treatment of benign tumors with a propensity for recurrence (craniopharyngiomas). For some benign lesions, there is a role for “wait and watch” until the child is older and more suitable for surgery.

Anatomical Access

Although similar surgical principles apply to adult and pediatric patients, access is limited in smaller patients, and the surgical approach must take into account the potential disruption of growth centers. Despite smaller nares and nasal cavities, most patients older than 4 years have sufficient room for standard endoscopic surgery. If not, a transoral or sublabial approach, such as midfacial degloving in combination with endoscopy, can be used to access the nasal cavity. Incomplete sinus pneumatization in the pediatric population can make the identification of normal anatomical structures more difficult. Cosmetic issues are a concern for both young patients and their parents, and reconstruction options are more limited because of incomplete facial growth and cosmesis. Disparate rates of development between the cranium and facial skeleton decrease the surface area of the nasoseptal flap relative to the anterior cranial base up to approximately 14 years of age.⁶

Blood Loss

The small size of pediatric patients is associated with smaller blood volumes. Hemostasis needs to be meticulous, and intraoperative blood loss is a particular challenge in patients with vascular tumors, bleeding disorders, or a religious aversion to blood products. Strategies to minimize blood loss include preoperative embolization, intraoperative ligation of feeding vessels, and the use of hemostatic materials and instruments. The staging of surgeries is often necessary in such patients to limit the intraoperative blood loss to less than one blood volume at each operation.

Malignant Tumors

Oncologic principles are the same in the pediatric population. The goals of surgery are complete resection of the tumor with the preservation of critical neurovascular structures. The most common malignancies in the pediatric population are sarcomas, and the role of surgery is limited to biopsy and the palliation of symptoms in most cases.

Craniofacial Disruption

A significant concern in pediatric skull base and craniofacial surgery is to avoid disruption of the permanent dentition within the maxillary complex during maxillotomy.²³ Permanent tooth eruption generally occurs after 10 years of age. The Le Fort I down-fracture approach is best avoided, and a presurgical dental panoramic X-ray or coronal CT scan is helpful to plan osteotomies to avoid injury to the tooth buds. With respect to open approaches, midfacial degloving and transmaxillary approaches afford wide exposure and the resection of sinonasal tumors with preservation of normal tooth eruption.

The possibility of skull and craniofacial osteotomies having an impact on the growing head and face is of major importance. A review of patients undergoing craniofacial resection, the youngest of whom was a 2-year-old child, showed normal craniofacial development up to 36 months postoperatively.²³ Longitudinal studies assessing the impact of various external and endonasal approaches on craniofacial growth are needed.

44.6 Specific Skull Base Pathology and Surgical Considerations

44.6.1 Midline Frontonasal Masses

Although they are rare, nasal dermoids, epidermoids, nasal gliomas, and meningoencephaloceles comprise the vast majority of these lesions. Of these, nasal dermoids are the most common, accounting for approximately 61% of congenital midline nasal masses.² The main clinical entities in the differential diagnosis include nasal glioma, encephalocele, and rarely hemangioma, lymphangioma, fibroma, lipoma, lipoblastoma, hairy teratoid polyp, dacrocystocele, and dacrocystitis. A nasal glioma is heterotopic, mature glial tissue (astrocytes and connective tissue) without a true capsule, found within or around the nose. A fibrous stalk representing the intracranial

connection can be found in 15% of cases. Nasal gliomas occur as an extranasal mass along the nasal dorsum in 60%, as an intranasal mass (lateral nasal wall, middle turbinate, nasal septum) in 30%, and in both locations in about 10% of patients.

Surgical resection is the treatment of nasal dermoids and is discussed elsewhere in this text. Although there is very little published literature on endoscopic techniques for the treatment of nasal dermoids, extensive endoscopic experience with lesions in the same area suggests that the same techniques can be applied. Initial experience, including our own, is supportive of endoscopic endonasal surgery for nasal dermoids with intracranial extension.²

Encephaloceles are defects in the skull and dura with herniation of intracranial contents. The most common etiology in children is a developmental anomaly causing the skull defect, and brain tissue (meningoencephalocele) is almost always present. Although rare, congenital meningoencephaloceles are more likely to contain critical vessels or specific neural structures, including the pituitary gland. Acquired defects are most commonly posttraumatic. The surgical treatment of these lesions is covered in detail elsewhere in the text.

44.6.2 Sellar and Parasellar Lesions

The differential diagnosis of pathology in this area includes numerous entities: cystic lesions (Rathke cleft cyst, arachnoid cyst), benign tumors (pituitary adenoma, craniopharyngioma, meningioma, hemangioma, ependymoma), inflammatory and metabolic lesions (hypophysitis, pituitary hyperplasia, fibrous dysplasia, sphenoid sinus mucocele, amyloidosis), and malignancy (pituitary carcinoma, germinoma, chordoma, chondrosarcoma, sinonasal malignancy, osteogenic sarcoma, fibrosarcoma, and metastasis).

Common pathology in this region includes Rathke cleft cysts, pituitary adenomas, and craniopharyngiomas. These lesions have a common embryologic development from primitive stomodaeum (Rathke pouch and duct); however, they differ in pathology and cell of origin (see section on developmental anatomy). The Rathke cleft cyst is a nonneoplastic lesion, whereas pituitary adenomas and craniopharyngiomas are benign neoplasms.

Rathke Cleft Cysts

Rathke cleft cysts can occur in the pediatric population, and it is imperative to distinguish these from cystic pituitary adenomas and craniopharyngiomas. The CT and MR findings are often variable and nonspecific, and it can be difficult to distinguish these lesions. A small, nonenhancing intracystic nodule is considered pathognomonic.³⁶ Most incidentally discovered Rathke cleft cysts are treated conservatively, and treatment is required only in patients who develop clinical symptoms (headache) or demonstrate progressive enlargement. The authors' preferred treatment strategy is via an endoscopic transsphenoidal transsellar/infrasellar approach to fenestrate the cyst and exteriorize the cyst wall. Maximal pituitary gland is preserved by fenestrating the floor of the cyst. Removal of the cyst lining is not necessary and risks a CSF leak.

Pituitary Adenomas

Pituitary adenomas are rare in children and account for 3% of supratentorial masses. They are more likely to be functioning adenomas, in which the most common histology is prolactinoma, followed by corticotropinoma and somatotropinoma.³⁷ Nonfunctioning adenomas, thyroid-stimulating hormone (TSH)-secreting adenomas, and gonadotropin-secreting adenomas constitute 3 to 6% of childhood pituitary adenomas.

Surgery is indicated for almost all histologic types of adenomas with the exception of prolactinoma, which can be successfully managed medically. The preoperative evaluation should include an endocrine work-up, visual field evaluation, and MR imaging with contrast. The goal of surgery is total resection with normalization of the endocrinopathy. An endoscopic endonasal transsellar approach to the pituitary gland achieves complete tumor removal in up to 100% of cases³⁸ with minimum morbidity compared with traditional microscopic transphenoidal approaches.^{38,39} Radiation is avoided in children.

Craniopharyngiomas

Craniopharyngioma is the most common benign pediatric tumor involving the sellar and parasellar region. It comprises up to 50% of sellar tumors and is of epithelial origin. The treatment challenges posed by these tumors are covered separately in the text. The endonasal approach offers a direct, anterior midline surgical pathway to the site of these tumors. Preinfundibular tumors may be removed via a suprasellar, transplanum approach with dissection in a caudal–cranial direction to the supracistern space. Transinfundibular tumors in the subchiasmatic space can be managed via a transsellar approach, and retroinfundibular tumors via a transsellar, pituitary transposition approach with dissection in an anteroposterior angle to the interpeduncular cistern.⁴⁴ However, a significant concern with pituitary transposition is pituitary dysfunction.⁴⁵ In addition, the endonasal approach alone is not suitable for large tumors with extensions beyond the interpeduncular cisterns, and these are best managed with a combined endonasal and open (pterional) or completely open approach.

44.6.3 Fibrous Dysplasia

Fibrous dysplasia is a nonneoplastic condition that results in the intramedullary accumulation of fibrous tissue and immature woven bone in a single (monostotic) or multiple (polyostotic) bones. It is due to an arrest of bone stromal cell differentiation, causing immature cells to proliferate and produce the masses of fibro-osseous tissue characteristic of fibrous dysplasia. McCune-Albright syndrome is a separate condition with several phenotypes and encompasses polyostotic bone involvement, endocrinopathy, and skin discoloration. The natural histories of these conditions are different. Craniofacial involvement occurs almost invariably with the polyostotic form, and the ethmoid bone is most commonly involved, followed by the sphenoid and frontal bones and the parietal, temporal, and occipital bones. Most of the common clinical problems are due to craniofacial asymmetry, pain, and cranial nerve compression. Secondary lesions, depending on the location of fibrous dysplasia, may also be symptomatic: mucocoeles, cystic fibrous dysplasia, hemorrhage, and aneurysmal bone cysts.

In most cases, the diagnosis can be confirmed radiographically.⁴⁶ CT demonstrates an expansile lesion with a fairly homogeneous appearance. There may be hypodense areas or cysts within the lesion. Despite a large mass, the bony growth respects cortical bone and neural foramina; the calvaria is expanded outward, and narrowing of foramina is rare. MR imaging demonstrates low-to-intermediate signal intensity on T1-weighted images and low signal intensity on T2-weighted images, although cartilaginous areas will appear very bright. A common scenario is a child who has MR imaging for unrelated reasons and the doctors are alarmed by a large skull base mass. In such cases, CT is helpful. Biopsy is not necessary to establish a diagnosis if the imaging is consistent with fibrous dysplasia.

Treatment goals depend on several factors. The natural history is an important consideration; it is now evident that fibrous dysplasia can occur after adolescence and progress into adulthood. Polyostotic disease has a higher rate of progression. The rate of malignant transformation (fibrosarcoma, osteosarcoma) is reported to be 0.4%, especially with radiation exposure.⁴⁶ Generally, treatment is reserved for symptomatic patients. Clinical and radiologic follow-up is sufficient, and surgery is considered when disfigurement, cranial neuropathies (including visual loss resulting from optic nerve compression), and pain occur. Although medical treatments with bisphosphonates have been used, the response rate is mixed because of selection bias, and long-term data are lacking. Corticosteroid treatment is reserved for patients with acute visual symptoms before surgery. Headaches do not typically resolve with surgery, and medical therapy should be pursued first.

Surgical intervention is the mainstay of symptomatic fibrous dysplasia. Overall, reports indicate a lower recurrence rate with the complete removal of fibrous dysplasia; however, the extent of surgery depends on the predicted morbidity due to surgery. A useful algorithm for deciding on the extent of surgery, proposed by Chen et al, classifies patients into four major groups according to the area affected: zone 1—fronto-orbital, zygomatic, upper maxillary; zone 2—hair-bearing cranium; zone 3—central cranial base; zone 4—teeth-bearing regions of the maxilla and mandible.⁴⁷ Total resection is suggested for zone 1 and partial resection for zones 2 through 4. Most sinonasal lesions can be completely removed with endoscopic sinus surgery, and skull base lesions are treated with either endoscopic or open approaches (depending on the location and extent of the lesion).

The optic canal is involved in up to 90% of sphenoid bone lesions. Available data indicate that asymptomatic individuals with optic nerve involvement are best managed conservatively, as up to 97% patients had stable vision without surgery.⁴⁶ Surgery carries its own risk for visual deterioration; 87% of asymptomatic patients who underwent prophylactic decompression and 65% of symptomatic patients who underwent surgery had stable long-term vision. If needed, optic nerve decompression can be performed safely with an endoscopic endonasal approach, and partial decompression is often sufficient. Any surgical intervention in patients with fibrous dysplasia is difficult because of the loss of normal anatomical landmarks and risk for neurovascular injury. Surgery should be undertaken by an experienced team with neurophysiologic monitoring and radiologic image guidance.

44.6.4 Paranasal Sinus Mucoceles

A paranasal sinus mucocele is an epithelium-lined sinus cavity filled with mucus secretions that results from obstructed sinus outflow. Its ability to expand by resorption and remodeling of the adjacent bone distinguishes it from a blocked sinus filled with trapped mucus. As it expands, it can erode into the adjacent orbit and skull base. It is rare in children, and predisposing factors include trauma, acute and chronic sinusitis, nasal polyps, cystic fibrosis (with nasal polyps), fibrous dysplasia, and iatrogenic causes (postoperative).⁴⁹ It is important to exclude underlying benign and malignant nasal and sinus lesions, including meningocele, neuroblastoma, lymphoma, and rhabdomyosarcoma. Mucoceles in children are often unilateral and affect the frontoethmoid region, followed by the maxillary sinus, sphenoid sinus, and posterior ethmoid sinus.

The preferred treatment option is intranasal endoscopic surgery and drainage. The wall of the mucocele is removed widely with preservation of the lining mucosa. Recurrence is uncommon and can be further managed endoscopically. Complex cases may have to be managed with a combination of open and endoscopic approaches.

44.6.5 Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) is a highly vascular, benign lesion found almost exclusively in males between the ages of 12 and 21 years. JNAs have extensive vascular and fibrous stromal components, and the cells of origin of these components are still debated. Recent evidence indicates that JNA is likely to be a vascular malformation or a hamartoma, derived from incomplete regression of the artery of the first branchial arch, rather than a true neoplasm.⁵⁰ JNA is more prevalent in patients with familial adenomatous polyposis. A hormonal pathogenesis is suggested; however, this remains controversial.

Anatomically, the site of origin lies in an area superior to the sphenopalatine foramen, which some authors consider to be in the pterygopalatine fossa at the level of the vidian canal aperture. The tumor is locally aggressive and from its origin enlarges in a submucosal plane into adjacent anatomical sites and involves the basisphenoid. From the pterygopalatine fossa, it may grow medially (nasal cavity, nasopharynx, and opposite side), anteriorly (toward the maxilla), anterosuperiorly through the inferior orbital fissure (orbital apex), laterally (pterygopalatine fossa to the infratemporal fossa), or posteriorly (root of the pterygoid canal). Intracranial extension is seen in 10 to 20% of patients, and this may occur through direct bone erosion or extension along the pterygoid canal, foramen rotundum, or superior orbital fissure. True dural invasion and intradural disease are rare.

Nasal obstruction and recurrent epistaxis are common presenting symptoms, and in advanced disease, facial deformity can be appreciated. Surgery is the treatment of choice, and CT and MR imaging are useful to delineate the extent of disease for surgical planning. Tumor vascularity poses a significant surgical challenge, and the degree of intraoperative blood loss may influence how much tumor can be resected at any one time. Blood supply is mainly from the internal maxillary artery branches, which can be embolized successfully; however, many intermediate and large tumors derive a significant blood supply

from the ICA (vidian artery and cavernous branches), which precludes effective embolization. Residual vascularity from the ICA is correlated with increased intraoperative blood loss, difficult surgical resection, and the need for multiple surgeries to achieve complete resection. A new staging system based on residual vascular supply has been proposed that provides better prognostication and facilitates preoperative planning.⁵¹

Surgical resection has traditionally been performed via transfacial (lateral rhinotomy, Weber-Ferguson), midface degloving incisions, and, for intracranial components, lateral (pterional craniotomy) approaches. In the past decade, endoscopic transnasal ± transmaxillary (via a Caldwell-Luc) approaches have been used to achieve complete resection of extensive, multi-compartmental, and intracranial lesions. An anterior endoscopic endonasal or endoscopically assisted approach provides access to all routes of tumor extension, both medial and lateral to the cavernous ICA. Incomplete resection of areas of skull base erosion or intracranial extension can be observed for regrowth. Most small residual tumors do not progress and involute over time. In our opinion, there is no role for radiation therapy. Regrowth of residual tumor can be treated endoscopically in most cases. Currently, many authors agree that the vast majority of JNAs, including those with intracranial involvement and significant lateral extension, can be surgically removed without an open approach. ▶ Fig. 44.5 shows a large JNA with intracranial extension that was resected in two stages, including a combined endoscopic and open approach.

Patients should be monitored clinically and with imaging for recurrence. It is generally agreed that surveillance for recurrence can be safely terminated when the patient reaches the early to mid 20s, after the end of adolescence.

44.6.6 Malignant Neoplasms

Malignant neoplasms are uncommon in the pediatric population. A multicenter review of patients younger than 21 years treated for malignancy showed a bimodal age distribution, peaking at 3.5 years and 17.5 years.⁵² High-grade sarcomas (including osteosarcoma, fibrosarcoma, rhabdomyosarcoma, Ewing sarcoma) and squamous cell carcinomas were the most common pathology, followed by esthesioneuroblastoma, low-grade sarcoma, chordoma, and salivary gland malignancy. Histology is the most important predictor of overall survival. A poor prognosis was associated with squamous cell carcinoma and salivary gland malignancies; an intermediate prognosis (60 to 70% 5-year survival) was associated with high-grade sarcoma, esthesioneuroblastoma, and chordoma; and the best prognosis was in low-grade sarcoma. It is interesting that radiation therapy before surgical therapy was associated with a poorer prognosis; however, this must be interpreted with caution because the indications for radiation therapy were not defined, and it is likely that these were tumors considered to be inoperable upon presentation.⁵²

Rhabdomyosarcoma

Sinonasal malignancies are rare in children and constitute a diverse group of pathologies with varying biological behavior. Rhabdomyosarcomas comprised more than 70% of maxillary sinus tumors, and 34% of tumors overall, followed by squamous

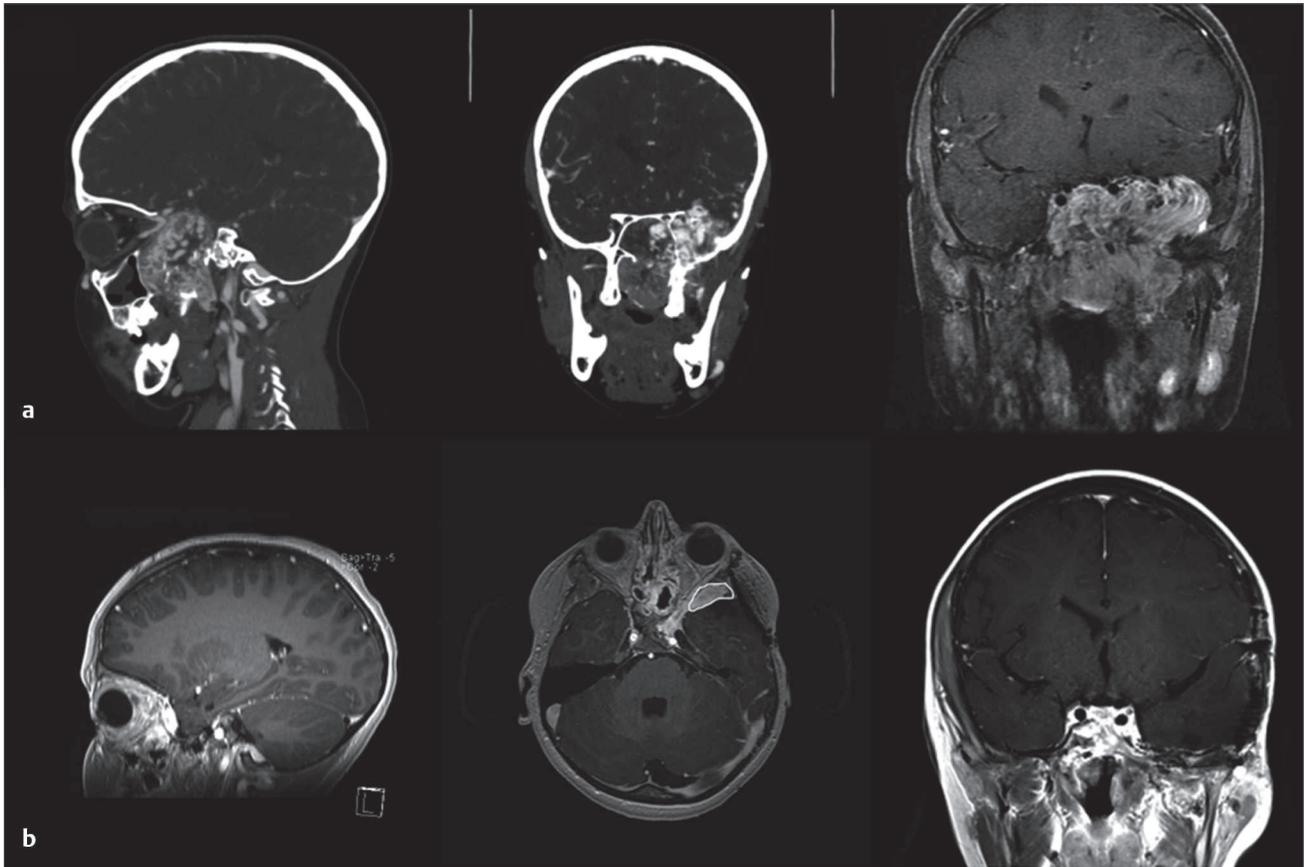


Fig. 44.5 (a) Coronal and sagittal reconstructions from pre-embolization CT angiography and coronal postcontrast T1-weighted imaging of a juvenile nasopharyngeal angiofibroma with intracranial extension that was resected in three stages: a combined pterional and endoscopic endonasal approach and two endoscopic endonasal approaches. (b) Sagittal, axial, and coronal postcontrast T1-weighted images 1 year after resection. On the axial image, a small residual superolateral to the orbit is circled in white. This has remained stable.

cell carcinomas and esthesioneuroblastomas. Rhabdomyosarcomas arise from striated muscle in the head and neck, and more than 50% are diagnosed primarily in the first decade of life. About 40% are located in the head and neck, and these are further divided into three major groups depending on their location: orbital, nonorbital parameningeal (nasal cavity, sinuses, ear, mastoid, pterygopalatine and infratemporal fossae), and nonorbital nonparameningeal (tongue, palate, and other head and neck sites). There are also three major histologic subtypes: embryonal, alveolar, and anaplastic. Tumors in orbital and non-orbital nonparameningeal sites and with embryonal histology (more common in children) have the most favorable prognosis.⁵⁴ Children with tumors in parameningeal sites often present with advanced disease. Overall, the extent of disease at presentation is the best predictor for survival.

A combination of surgery, radiotherapy, and chemotherapy has shown the best survival outcomes for head and neck rhabdomyosarcomas (5-year survival rates of 25 to 83%)⁵⁵ and for paranasal sinus tumors (70%).⁵⁶ The local and regional recurrence rate is reported to be 43%.⁵⁶ Although surgery is considered a valuable treatment in this disease, its role is thought to be limited in those with parameningeal skull base sites because of risks to critical neurovascular structures and morbidity. Endoscopic endonasal approaches can offer a less

morbid option; however, data for surgery at these sites are currently lacking. At present, the role for surgery is in diagnosis, follow-up, and salvage. A recent study showed a prognostic value of debulking surgery, with which the complete response rate was higher.⁵⁷ Orbital tumors have an excellent prognosis with chemoradiotherapy, and the role for surgery is limited to biopsy.

Chordoma

Chordomas are malignant osseous neoplasms arising from remnants of the embryonic notochord and can occur anywhere along the axial skeleton. Three histologic subtypes are described: classic, chondroid, and dedifferentiated. The classic subtype consists of physaliphorous tumor cells with vacuolated cytoplasm, which gives it a “bubbly” appearance, and the chondroid type has features of chordoma and chondrosarcoma. The most common site in children is the skull base, usually the clivus. Chordomas are generally slow-growing, locally aggressive tumors, and metastasis is seen in 10 to 20% of patients, although a rate as high as 43% is reported from autopsy studies. Younger patients can have more aggressive disease, with rapid growth rates and a poor prognosis. Intradural disease is rare. Disseminated disease is a late finding, and control of the primary site is the principal therapeutic goal.

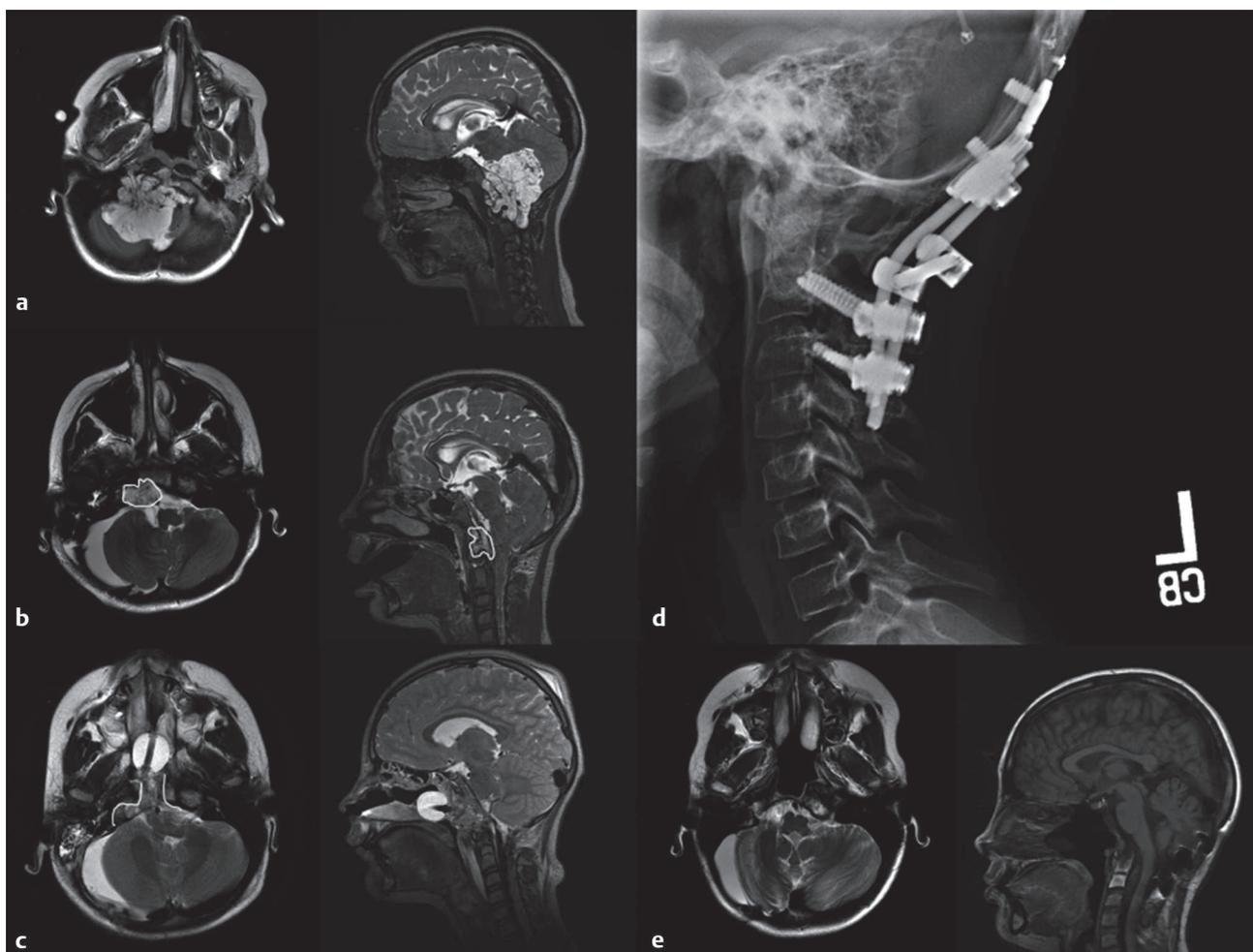


Fig. 44.6 (a) Preoperative axial and sagittal T2-weighted images of a large chordoma. (b) Axial and sagittal T2-weighted images after a far lateral approach. Areas of residual tumor are outlined in white. (c) Axial and sagittal T2-weighted images after an endoscopic endonasal approach for residual tumor involving the clivus and C1–2 joint space. The surgical corridor is outlined in white on the axial image. (d) Occipital cervical fusion was performed after complete resection of the right condyle via far lateral and endoscopic endonasal approaches. (e) Axial T2-weighted image and sagittal FLAIR (fluid-attenuated inversion recovery) image 2 years after resection and proton beam therapy. Radiation changes can be seen in the dens.

Surgery with the goal of complete resection is the primary treatment. The endoscopic endonasal transclival approach is the most direct approach with which to access these tumors. The locally aggressive biology of the tumor makes complete resection a challenge, especially given the close proximity to critical neurovascular structures, including the ICA. Large tumors may require staged surgeries with multiple approaches. ▶ Fig. 44.6 shows a large chordoma resected with a combined open and endonasal approach. Overall average survival is 54% at 5 years, and a worse prognosis is seen in patients younger than 5 years old.⁵⁸ Survival rates were not shown to be significantly different based on the histologic subtype or treatment type (surgery alone or surgery followed by radiotherapy). Radiotherapy is recommended for patients with large tumors and those with less than gross total resection. Diverse radiation treatments have been proposed; proton beam therapy has theoretical advantages compared with standard radiotherapy modalities. In a small retrospective review, the authors proposed a role for chemotherapy (etoposide and ifosfamide) following surgical resection.⁵⁹

44.7 Postoperative Management and Complications

In the immediate postoperative period, antibiotic therapy is continued for 24 hours or until all nasal packing is removed. After endoscopic endonasal procedures with dural reconstruction, nasal packing is maintained for approximately 7 days. Early CT or MR imaging (while the patient is still sedated) is helpful in detecting intracranial complications and assessing the extent of tumor removal. The postoperative management of children is more problematic because of noncompliance with office procedures. Removal of nasal splints and packing, repeated nasal debridement, and imaging studies may require general anesthesia. The management of medical issues such as pituitary dysfunction (hypopituitarism, diabetes insipidus) may delay discharge.

The complications associated with cranial base surgery are myriad and can be life-threatening or trivial, temporary or permanent. There is no standardized classification of skull base complications. A list of possible complications is provided in

Table 44.7 Potential complications of skull base surgery

Category	Incidence	Consequences
Vascular injury (P1 perforator, pontine bleed, internal maxillary artery, frontopolar avulsion, ophthalmic artery, internal carotid artery)	0.9%	Death (0%) Transient deficit (0.1%) Permanent deficit (0.4%) No deficit (0.4%)
Neural injury (cranial nerves III, V ₁ , V ₃ , VI, IX, X, XII; hemiparesis)	1.8%	Permanent deficit (0.5%) Transient deficit (1.3%)
Infection (meningitis, intradural abscess, extradural abscess)	1.9%	Death (0.1%) Deficit (0.1%) Successfully treated (1.6%)
Systemic (pulmonary embolism, pneumonia, myocardial infarction, acute renal failure, respiratory failure, multiple-organ failure)	2.9%	Death (0.7%) Successfully treated (2.1%)
Delayed deficit (visual deficit, hematoma, hemiplegia, ataxia, proptosis)	1.9%	Permanent deficit (0.6%) Transient deficit (1.3%)

Source: Adapted from Kassam AB, Prevedello DM, Carrau RL, et al. Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients. *J Neurosurg* 2011;114(6):1544–1568.

► Table 44.7. For the purposes of this review, the more common complications are discussed.

44.7.1 Pituitary: Hypopituitarism, Diabetes Insipidus

Injury to the pituitary gland and loss of function may result from aggressive resection of tumor or loss of blood supply (superior hypophysial vessels). The effects of hypopituitarism will depend on the age of the patient but include cortisol deficiency, hypogonadism, and hypothyroidism. Endocrinologists are involved in the perioperative management of these patients, and hormonal replacement therapy can be instituted. In patients who are at risk for cortisol deficiency, stress steroids are administered perioperatively.

Diabetes insipidus is a consequence of injury to the posterior gland or hypothalamus. It is characterized by a sudden increase in urine output because of impairment in the secretion of antidiuretic hormone. During the postoperative period, urine output of more than 2 to 3 mL/kg for 2 consecutive hours is suggestive of diabetes insipidus. Manifestations include polyuria, dehydration, hypovolemia, and polydipsia. The diagnosis is confirmed if the serum level of sodium exceeds 145 mEq/L, the urine is dilute with a specific gravity of less than 1.005, and the urine osmolality is between 50 and 150 mOsm/kg. The treatment of mild diabetes insipidus includes fluid and electrolyte replacement. The administration of DDAVP (deamino-8-D-arginine vasopressin, desmopressin acetate) is indicated when diabetes insipidus is persistent, dehydration and electrolyte disturbances are severe, or the patient is uncomfortably polydipsic or polyuric. In the postoperative period, diabetes insipidus usually is a self-limited condition, and pharmacologic treatment tends to be temporary.

44.7.2 Cerebrospinal Fluid Leak/Pneumocephalus

A CSF leak occurs in up to 5% of patients undergoing endonasal cranial base surgery and is one of the most frequent major

complications. Risk factors for a CSF leak include patient demographics, patient comorbidities, diagnosis, location and size of dural defect, method of reconstruction, and perioperative management. Younger and older patients appear to be at increased risk, but this may be due to other related factors. Morbidly obese patients have elevated CSF pressures. Similarly, patients presenting with a spontaneous CSF leak and those with significant mixing of blood and CSF have elevated CSF pressures postoperatively. In our experience, patients with craniopharyngiomas have an increased risk for CSF leak that may be a consequence of a high-flow defect as well as transient hydrocephalus from the cyst contents. Large dural defects and those that communicate with CSF cisterns or ventricles pose a greater risk. Successful repair of dural defects has been achieved with a variety of nonvascularized and vascularized tissues. The use of vascularized septal flaps and pericranial flaps has decreased the incidence of postoperative CSF leaks to less than 5%. Although lumbar spinal drainage is often used to treat minor CSF leaks, the routine use of CSF diversion to prevent a postoperative CSF leak has not been convincingly demonstrated.

Usually, a postoperative CSF leak is readily apparent based on the symptoms (unilateral watery rhinorrhea, reservoir sign due to pooling of fluid in the sinuses, "double-ring" sign of blood-tinged drainage) and physical examination (endoscopic findings, Valsalva maneuver). Persistent postoperative pneumocephalus or increasing pneumocephalus implies a dural opening. In questionable cases, a postoperative CSF leak can be confirmed by testing collected fluid for β_2 -transferrin or beta trace protein (although the nasal passages can be contaminated in the immediate postoperative period) or by CT cisternography.

The aggressive management of postoperative CSF leaks is warranted to prevent the sequela of meningitis. For small leaks in the early postoperative period, lumbar spinal drainage can allow the leak to seal. CSF diversion can increase the risk for meningitis, however, because of reversal of flow. Prophylactic antibiotic therapy for CSF leaks is not recommended because of a lack of efficacy and the selection of antibiotic-resistant bacteria. Following endonasal skull base surgery, aggressive management with surgical intervention within 24 hours has been an

effective strategy. Lumbar drains are reserved for recurrent leaks, high-flow leaks, and patients with suspected elevated CSF pressure.

44.7.3 Infection/Meningitis

The incidence of meningitis following cranial base surgery is very low, with reports of 0.9 to 2.5% for transcranial surgery and 1 to 2% for endonasal skull base surgery.^{63–65} Surprisingly, endonasal approaches through a clean-contaminated environment have not been associated with an increased risk for infection. There is no consensus regarding the best regimen for antibiotic prophylaxis, but a single agent with moderate CSF penetration (e.g., a third- or fourth-generation cephalosporin) is sufficient. Factors that contribute to postoperative meningitis include active infection (sinusitis, wound infection), postoperative CSF leak, and the use of nonvascularized tissues for reconstruction. Factors that delay healing (malnutrition, Cushing disease, radiation therapy) may also contribute. Patients with sinusitis should be treated before surgery that transgresses the infected sinus. Early intervention for CSF leaks decreases the risk for delayed meningitis.

44.7.4 Vascular Injury

The risk for a vascular injury depends on multiple factors, including the extent of the pathology, experience of the surgeon, and region of dissection. Injury to small vessels can be as devastating as injury to the ICA. When tumors are dissected from the optic chiasm, the loss of small branches of the superior hypophysial artery can result in visual loss or hypopituitarism. Injury to small perforating vessels when tumors are dissected from the brainstem can result in stroke or hyperphagia syndrome. Tumors of the anterior cranial fossa that encase the anterior cerebral arteries pose a greater risk for dissection. Injury may result in memory and personality changes. Large tumors are internally debulked first to collapse the tumor and allow extracapsular dissection of the tumor margin without retraction. Pulling of tumor is avoided so that small vessels are not avulsed on the backside of the tumor. If tumor cannot be safely dissected from these small vessels, it is better to perform a partial resection.

Injury to the ICA is avoided with a detailed knowledge of skull base anatomy and good surgical technique. Bleeding from the ICA may result from the avulsion of small branches or direct injury. Small arterioles can be sealed with bipolar electrocautery. Larger injuries should be sutured if possible or controlled with the application of a crushed muscle patch. If this is not possible, intraoperative sacrifice of the ICA with packing or placement of aneurysm clips is usually necessary. Postoperative angiography should be performed in all of these patients to detect a pseudoaneurysm. Management includes insertion of a covered stent or angiographic sacrifice of the vessel. The adequacy of collateral cerebral circulation can be assessed with a combination of CT and MR imaging, angiography, and CT perfusion or SPECT (single photon emission computed tomography) balloon occlusion tests. If the collateral circulation is inadequate, a bypass graft from the carotid artery to the middle cerebral artery may be considered.

44.7.5 Neural Injury

Cerebral contusions are a direct consequence of brain retraction, and the surgical approach should be designed to minimize retraction. The incidence of radiographic encephalomalacia is as high as 60% of patients undergoing transcranial surgery of the anterior cranial base. The risk for contusion is increased if there is preoperative cerebral edema secondary to tumor disruption of the blood-brain barrier.

Cranial nerve injury is a consequence of manipulation or ischemia. Surgical approaches should be designed to minimize the manipulation of nerves, and small vessels to the nerves from the cranial circulation should be preserved. The sixth cranial nerve is particularly susceptible to injury because of its long course and small diameter. It can be injured medial (brainstem) or lateral (Dorello canal) to the paraclival segment of the ICA. Neurophysiologic monitoring of the motor component of the cranial nerves and the use of intraoperative nerve stimulation decrease the risk for permanent injury. The sacrifice of cranial nerves is often necessary because of tumor involvement. Care should be taken to avoid loss of the first division of the trigeminal nerve in association with the vidian nerve because the combination of corneal anesthesia and decreased tearing places the cornea at high risk for ulceration. Loss of the vidian nerve is generally well tolerated in young patients (loss of emotional tearing) but may contribute to a dry eye in older patients with decreased baseline tearing.

44.7.6 Craniofacial Growth

The growth of the facial bones lags behind the development of the cranium. Skeletal maturation of the skull shape and size first occurs at the skull base at approximately 12 years, followed by facial maturation at approximately 16 years.⁷ Extensive surgery of the craniofacial skeleton and radiation therapy disrupt growth centers and result in facial asymmetry as the child develops. Surgical approaches should be designed to minimize dissection of periosteum and the disruption of potential growth centers. Endoscopic endonasal surgery may limit the effects of surgery on facial growth, but long-term data on its effects on nasal and midfacial development is lacking. Although nasal septal flaps can be employed for the reconstruction of dural defects in children, they are smaller relative to the anterior cranial base in children younger than 14 years. We have not observed adverse effects on nasal growth, but experience is limited.

44.8 Quality of Life

Studies of postoperative quality of life that use the anterior skull base questionnaire in patients undergoing anterior craniofacial resection for sinonasal malignancy demonstrate good function across all domains.⁶⁶ In patients undergoing endoscopic endonasal surgery of the skull base, excellent quality of life scores are noted when the anterior skull base questionnaire is used.⁶⁷ Limited data suggest that quality of life is superior to that after open transcranial approaches. Nasal morbidity has been assessed in the endonasal surgical group with the Sino-Nasal Outcome Test (SNOT-22), a validated instrument. As expected, increasing nasal morbidity (decreased quality of life)

was noted in the nontranssellar sagittal plane and coronal plane surgical modules compared with transsellar surgery.

44.9 Conclusion

Cranial base surgery is a rapidly evolving subspecialty that requires a vast knowledge of anatomy and encompasses a wide variety of pathologies and surgical approaches. The same principles apply to pediatric and adult populations. Cranial base surgery is best practiced by teams of surgeons with expertise in open and endonasal approaches. Morbidity is acceptable and overall quality of life is good following cranial base surgery. Good oncologic outcomes can be obtained for a variety of benign and malignant neoplasms.

Technological advances will continue to drive advances in pediatric skull base surgery. The increased adoption of minimal access approaches such as endoscopic endonasal surgery requires training programs that provide an incremental and standardized approach to training.⁶⁸ Because of the rarity of skull base pathology, multi-institutional studies of outcomes are necessary to answer basic questions about outcomes and quality of life.

Pearls

- Approaches to skull base tumors should not cross vascular or neural structures.
- Combined approaches should be considered to avoid crossing vascular and neural structures.
- Multidisciplinary teams are beneficial in addressing the varied needs of these challenging cases.
- In young children, a watch and wait approach may be appropriate for benign lesions.
- Minimizing the disruption of growth centers should be considered when planning surgical approaches in young children.
- Skull base reconstruction should be vascularized whenever possible and planned as part of the surgical approach.
- CT-based image guidance can prove invaluable when accessing non-pneumatized sinuses or other cranial base structures in children.
- The embryology and anatomic origin of pediatric skull base and pituitary tumors often makes them most suitable for a midline approach such as the endoscopic endonasal approach.

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45 Spinal Extradural Neoplasms and Intradural Extramedullary Neoplasms

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Central nervous system (CNS) tumors are responsible for 24% of cancer-related pediatric fatalities, and 5 to 10% of these tumors arise in the spinal axis.¹⁻³ The ratio of intraspinal tumors to intracranial tumors is smaller in the pediatric than in the adult population, with estimates ranging from 1:5 to 1:20.⁴⁻⁹ Spinal neoplasms may be primary lesions arising within the spinal axis, secondary lesions resulting from extraspinal contiguous spread, or rarely, metastatic lesions.⁴ Neoplasms are categorized according to the space they occupy: extradural, intradural extramedullary, or intramedullary.^{1,2,4}

This chapter features a discussion of the epidemiology, pathology, presentation, and treatment for pediatric extradural and intradural extramedullary neoplasms.

45.1 Epidemiology

Whereas several series show an equal distribution of spinal lesions in boys and girls, others report a predominance in boys.⁵⁻¹³ An increased rate among boys may relate to the inclusion of congenital lesions, which predominate in boys.⁶ Up to 12% of spinal tumors have been reported to arise in the first year of life; these tumors include lipomas, teratomas, and neurenteric cysts.⁴ Neuroblastomas commonly extend to the epidural compartment and cause a mass effect in early childhood, resulting in 12 to 30% of cases of neoplastic cord compression in this age group. Intradural extramedullary spread may occur at any age, although the metastasis of intracranial lesions like medulloblastoma, ependymoma, choroid plexus carcinoma, and retinoblastoma usually occurs within the first decade.⁴ Excluding congenital lesions, tumor occurrence is evenly distributed throughout the first 15 years of life.¹⁴

► Table 45.1 summarizes the various types of neoplasms, both intramedullary and extramedullary, found in the spinal canals of 649 pediatric patients in 10 large series published between 1953 and 1990.^{5-8,10-12,15-17} ► Table 45.2 reviews the anatomical distribution of intraspinal tumors in 413 pediatric patients, with the predominance of tumors arising in the thoracic and lumbar region.⁶⁸ The statistics reported in these large series must be examined carefully, as they often include developmental abnormalities that are not true neoplasms.

► Table 45.2 shows the distribution of tumors, both intramedullary and extramedullary, along the spine. Tumors are distributed fairly evenly throughout the cervical, thoracic, and lumbar spinal regions. The thoracic spine and lumbar spine are the sites of 20.5% and 23%, respectively, of pediatric spinal tumors. This distribution is in contrast to the thoracic predominance of spinal neoplasms seen in adults.⁴ Sacral tumors are less common, and many of the tumors reported to arise in the lumbosacral region may be masses of developmental origin and not true neoplasms.

45.2 Pathology and Pathobiology

45.2.1 Intradural Extramedullary Neoplasms

In adults, tumors in the intradural extramedullary compartment are the most common intraspinal tumors. In children, they account for approximately 25% of intraspinal tumors (► Fig. 45.1 and ► Fig. 45.2). Dermoid and epidermoid tumors comprise about one-third of these lesions, originating in sinus tracts that form during faulty separation of the neuroectoderm from the overlying cutaneous ectoderm at the time of disjunction. Meningiomas are common tumors in adults but account

Table 45.1 Tumor types in 649 pediatric patients in 10 large series

Location ^a	Tumor type	No. of patients	Total (%)
Intramedullary			189 (29.1)
	Astrocytoma	114	
	Ependymoma	50	
Intradural extramedullary	Lipoma	25	
			156 (24.0)
	Dermoid	39	
	Neurofibroma	28	
	Schwannoma	20	
	Meningioma	17	
	Epidermoid	14	
Extradural	Primitive neuroectodermal tumor	30	
	Hemangioepithelioma	8	
			233 (35.9)
	Sarcoma	67	
	Neuroblastoma	64	
Others	Teratoma	35	
	Metastasis	29	
	Ganglioglioma	19	
	Lymphoma	19	
			71 (10.9)

Source: Adapted from references^{5-8,10-12,15-17}.

^aSome of the teratomas, neurofibromas, and dermoid tumors arose from both intradural extramedullary and extradural compartments.

for fewer than 5% of tumors in children. Although psammomatous meningiomas are the most common type, hypercellular lesions with high mitotic rates occur more often in children than in adults, representing aggressive, sarcomatous lesions.^{18,19} Nerve sheath tumors, such as neurofibromas and schwannomas, account for about 10% of spinal tumors in children and about 30% of intradural extramedullary tumors. Meningiomas and tumors of the nerve sheath are often associated with neurofibromatosis types 1 and 2 (NF-1 and NF-2)²⁰. Myxopapillary ependymomas can also be intradural extramedullary tumors that develop at the filum, enveloping roots in the cauda and/or involving the conus (► Fig. 45.3).

Table 45.2 Levels of intraspinal tumors in 413 pediatric patients

Spinal Level	No. of patients	Percentage (%)
Cervical	80	19
Cervicothoracic	23	6
Thoracic	109	26
Thoracolumbar	48	12
Lumbar	87	21
Lumbosacral	29	7
Sacral	27	7
Holocord	10	2

Source: Adapted from Raffel C, McComb JG. Spinal cord tumors. In: Weinstein SL, ed. *The Pediatric Spine: Principles and Practice*. New York, NY: Raven Press; 1994:917–930.⁶⁸

45.2.2 Diffuse Subarachnoid Tumors

The rarest spinal lesions in children are diffuse subarachnoid or leptomeningeal tumors. They usually arise from the dissemination of a posterior fossa tumor along cerebrospinal fluid (CSF) pathways. CSF dissemination most commonly occurs in primitive neuroectodermal tumors (PNETs), germ cell tumors, ependymomas, and malignant gliomas.²¹ These tumors rarely present with spinal symptoms; however, 20% of PNETs in the posterior fossa show dissemination upon presentation.²² Subarachnoid dissemination of an intracranial tumor invariably leads to a poor prognosis.

Histologic grade influences the risk for leptomeningeal metastases in children with primary brain tumors. Civitello et al²³ reported a 2% incidence of leptomeningeal metastases in low-grade gliomas compared with a 33% risk reported in children with supratentorial high-grade gliomas.²⁴ Leukemia is one of the most common systemic malignancies to involve the CNS. Leukemic meningitis may occur either at the time of initial diagnosis (3%) or at the time of leukemic relapse (15%).^{25,26} Surgical approach is indicated only for tissue diagnosis.

45.2.3 Extradural Neoplasms

Thirty-five percent of intraspinal neoplasms in children are extradural. ► Table 45.3 summarizes the extradural pathologies reported in four series.^{15,27–29} Children younger than 3 years of age with an extradural spinal tumor were more likely to have a neuroblastoma/ganglioneuroma (► Fig. 45.4). Sarcoma was more common in patients older than 3 years.¹⁴ Cord compression develops in 3 to 5% of children with a systemic cancer.²



Fig. 45.1 An 11-year-old boy with neurofibromatosis type 2 presented with left leg weakness. (a) T2-weighted- and (b) contrast-enhanced sagittal magnetic resonance images of the cervical and upper thoracic spine exhibit a 2.5 × 3.5-cm homogeneously enhancing lesion ventral to the spinal cord centered at T4. Incidentally, there is also a contrast-enhancing intramedullary lesion at C2. The patient underwent a thoracic laminectomy with resection of this meningioma.

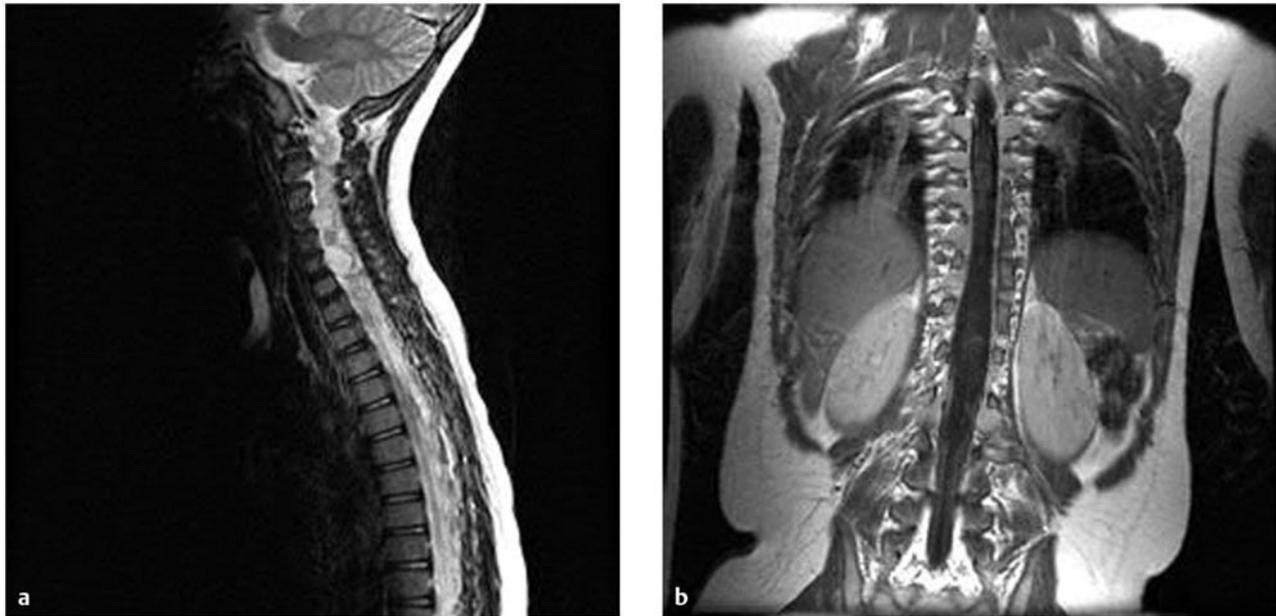


Fig. 45.2 (a) Sagittal and (b) coronal gadolinium-enhanced magnetic resonance images of the cervical and thoracic spine of a 6-year-old girl with neurofibromatosis demonstrate multiple enhancing tumors involving most nerve roots of the cervical and thoracic cord.

45.3 Signs and Symptoms

The clinical manifestations of extramedullary tumors vary with location and the involvement of neural elements and bony structures.³⁰ The onset of symptoms may be rapid, with acute paraplegia and spinal shock, and symptoms presenting for months or years before presentation. The symptoms may also develop following spinal trauma, as a result of increased edema.

In patients with extramedullary spinal tumors, weakness and pain are the most common presenting symptoms (► Table 45.4 and ► Table 45.5). The weakness is usually in the upper motor neuron distribution, with increased tone, hyperactive deep tendon reflexes, and extensor plantar reflexes (Babinski sign). If the conus medullaris or cauda equina is involved, asymmetric, flaccid weakness may occur. In infants and toddlers, the weakness may be subtle; failure to meet gross motor milestones, refusal to walk, irritability, and frequent urinary tract infections may result from spinal cord compression. At presentation, the incidence of weakness was found to range from 53 to 82% depending on the degree of cord compression.^{29,31,32}

Pain occurs most commonly in the back and is reported in 28 to 80% of patients.³¹⁻³³ Distention of the dural tube may cause vague back pain with palpable tenderness. The afferent nociceptive neurons are activated by both the mechanical distortion and the release of inflammatory mediators.^{4,33} Children may have radicular pain radiating into an arm, leg, or the chest wall. Radicular pain can be paroxysmal and spontaneous or provoked by motor or sensory stimuli. Pain with neck flexion or straight leg raise may indicate dural traction, and recumbency may exacerbate pain by altering canal and foramen size.³³ Back or radicular pain in a child with known malignancy requires immediate evaluation. In children without a known malignancy, a careful evaluation is required as to avoid

diagnostic delays.³³ Sensory disturbances are also common in patients with spinal tumors.^{29,31,32} In comparison with pain or temperature, fine touch is a more sensitive indicator of sensory level, although this is not critical with the current noninvasive imaging techniques.⁷

Bladder or bowel dysfunction is also common and occurs in one-half of patients with severe cord compression.²⁹ Changes in bladder function are difficult to detect in young children, especially before toilet training.⁶ Loss of bladder control in a toilet-trained child should raise the suspicion of a spinal lesion. Dysfunction of the bowel or bladder is found only through a careful neurologic examination, and formal urodynamic studies may be merited.

Scoliosis of the spine occurs in about one-fourth of children with spinal tumors and may be the initial presenting sign. In any child with a progressive abnormality of spinal curvature, the diagnosis of intraspinal neoplasia should be considered.^{4,6,7,12,34} Kyphosis is usually a late finding associated with extensive bony metastatic disease.

Patients with spinal tumors, especially malignant tumors, may have hydrocephalus and associated increased intracranial pressure (ICP).^{35,36} Decreased CSF absorption secondary to elevated CSF protein content may lead to hydrocephalus.³³ Patients with spinal cord tumors may have symptoms related to sequelae of their disease: infectious or radiation-related myelopathy, spinal cord stroke, intradural or extradural hematoma secondary to thrombocytopenia or coagulopathy, or an epidural abscess.

The most common nontraumatic acquired cause of paraparesis in children is malignant epidural spinal cord compression by epidural tumor deposits. Cord compression may be the presenting sign of malignancy in 28 to 76% of patients.^{15,27,31,32} These epidural deposits differ from those found in adults in their histologic features, the location and direction of compression, the

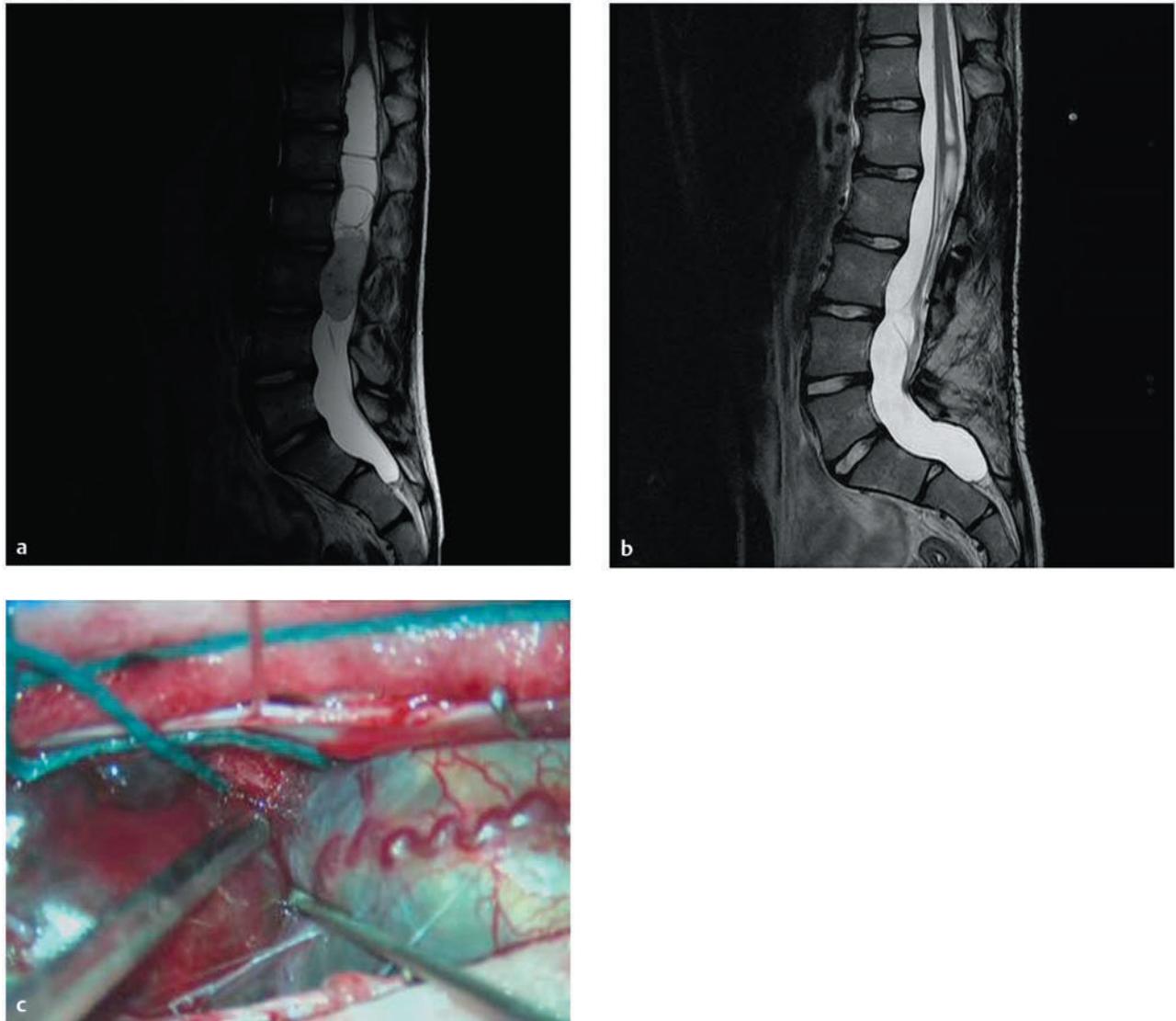


Fig. 45.3 A 14-year-old boy presented with progressive back pain. (a) T2-weighted magnetic resonance image shows a solid mass at the tip of the conus/proximal cauda equina. (b) Image after decompression and gross total resection of a myxopapillary ependymoma. (c) Intraoperative photograph.

degree of bone involved, and the general medical condition of the patient.^{27,31,37,38}

During early childhood, sympathetic tumors such as neuroblastoma and ganglioneuroma predominate. A series reported from St. Jude Children's Research Hospital concluded that 18% of children with Ewing sarcoma, 8% with neuroblastoma, and 7% with osteogenic sarcoma had compression of the spinal cord at some time during their disease.²⁸ In one series, 26% and 21% of cases of cord compression were secondary to neuroblastoma and Ewing sarcoma, respectively.³³ Malignant epidural spinal cord compression is the most frequent neurologic complication of Ewing sarcoma; sarcomas have a higher incidence of spinal cord compression and usually present at a slightly later age.^{27,39}

45.4 Diagnostic Studies

45.4.1 Plain Radiography

Plain radiographs of the spine are a reasonable first step in the evaluation of a patient suspected to have an intraspinal tumor. Plain radiographs show abnormalities in one-half of patients with spinal cord tumors.^{5,16} Intradural extramedullary tumors can thin or cause sclerosis of the pedicles. A tumor that extends through and enlarges a neural foramen is best visualized on oblique films. An enlarged foramen indicates a tumor of the nerve sheath or a paraspinous tumor. Malignant tumors and epidural metastases erode bone and may cause vertebral body collapse. The loss of a pedicle

through bony destruction causes the “winking owl” sign.⁴⁰ Plain radiographs are also important in the evaluation of and surgical planning for patients who present with spinal deformity. They are rarely of value in the evaluation of spinal cord compression. In one series, only 30% of children with metastatic spinal disease presenting with spinal cord compression had abnormal plain radiographs.²⁷ Abnormalities are more often detected in adults with cord compression, in whom most epidural invasion is from vertebral sites versus paraspinous sites in children.

Table 45.3 Extradural tumor type in 246 pediatric patients in four large series

Tumor type	No. of patients	Percentage (%)
Neuroblastoma	64	26
Ewing sarcoma	52	21.1
Rhabdomyosarcoma	31	12.6
Osteogenic sarcoma	29	11.8
Lymphoma ^a	19	7.7
Undifferentiated sarcoma	12	4.9
Germ cell tumor ^b	12	4.9
Leukemia	7	2.8
Wilms tumor	4	1.6
Other	16	6.5

Source: Adapted from references ^{15,22,27,28}.

^aHodgkin and non-Hodgkin. ^bEmbryonal cell carcinoma, endodermal sinus tumor, and teratoma.

45.4.2 Magnetic Resonance Imaging

Magnetic resonance (MR) imaging is the study of choice to identify spinal cord neoplasms. It provides anatomical detail while obviating the need for lumbar puncture, thus eliminating two risks: (1) bleeding from thrombocytopenia or coagulopathy and (2) acceleration of the rate of neurologic deficit from the loss of CSF. MR imaging is at least as sensitive as myelography combined with computed tomography (CT), providing superior anatomical details in and around the spinal canal.

MR imaging should be performed both with and without intravenous contrast enhancement (gadolinium diethylene-triamine-pentaacetic acid [Gd-DTPA]) and in multiple planes of view. In studies done without contrast, both T1- and T2-weighted images should be obtained. Usually, the surgeon is able to identify abnormal areas in the spinal canal without contrast; however, contrast is useful for defining the extent of tumor.

In a study of patients with documented intradural extramedullary disease, the administration of Gd-DTPA aided in the identification of 2- to 3-mm intradural extramedullary nodules and the demonstration of leptomeningeal spread.⁴ Larger intradural extramedullary lesions, such as nerve sheath tumors and meningiomas, are readily imaged within the subarachnoid space with standard imaging techniques, although the use of Gd-DTPA makes these lesions much more conspicuous and confirms the compartment and extent of the lesion (► Fig. 45.1). Lesions containing fat or cholesterol, such as dermoids, epidermoids, and lipomas, are visualized without the use of contrast.

Intradural extramedullary lesions often displace the cord contralaterally, widening the ipsilateral CSF space and creating

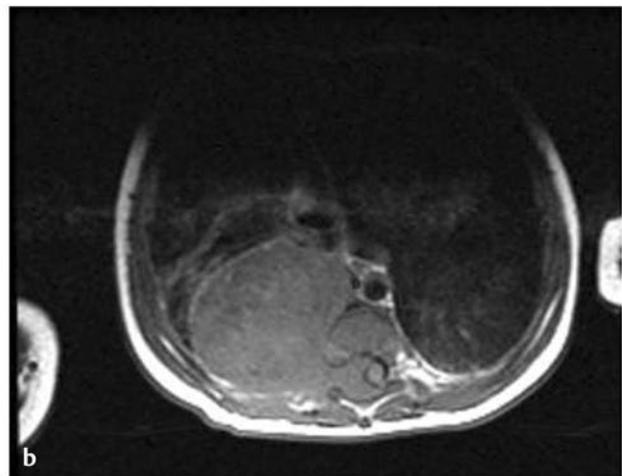
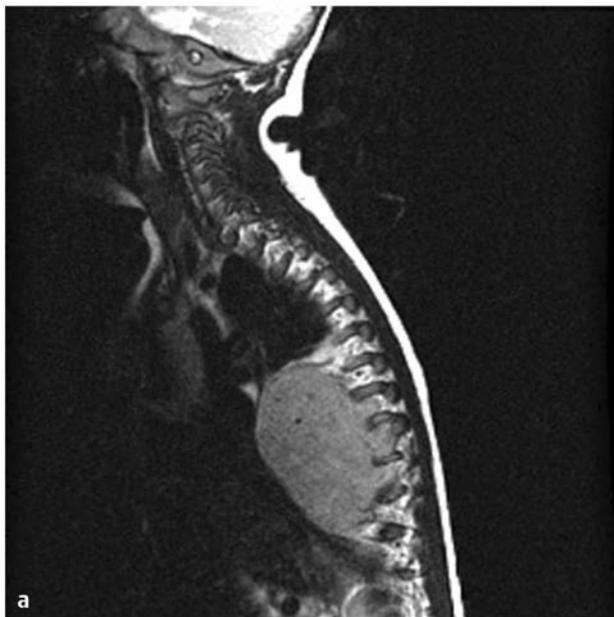


Fig. 45.4 A 5-month-old boy presented with chronic cough. (a) Magnetic resonance imaging demonstrates a large neuroblastoma with extraspinal and intraspinal components. (b) On T1-weighted axial image, the intraspinal component is extradural and compresses the spinal cord laterally to the left.

Table 45.4 Symptoms in 504 pediatric patients with intraspinal tumors

Symptom	No. of patients	Percentage (%)
Weakness	292	54
Back pain	150	30
Extremity pain	60	12
Incontinence	118	23
Muscle spasm	36	7
Sensory changes	22	4
Curvature	26	5
Mass	8	2
Meningitis	4	1
Hydrocephalus	4	1
Subarachnoid hemorrhage	2	1

Source: Adapted from Raffel C, McComb JG. Spinal cord tumors. In: Weinstein SL, ed. *The Pediatric Spine: Principles and Practice*. New York, NY: Raven Press; 1994:917–930.⁶⁸

what is known as the “meniscus” sign.⁴¹ In patients with extradural lesions, T1-weighted images provide adequate tissue contrast. The metastatic deposits are hypointense against the high signal of normal marrow and epidural fat. Metastatic lesions usually have an increased signal on T2-weighted images, but signal characteristics may vary because of hemorrhage, inflammatory debris, and necrosis. Intravenous Gd-DTPA may be helpful, although enhancement may make vertebral and epidural metastatic deposits less conspicuous; the signal is similar to that of normal epidural fat and vertebral marrow on T1 weighted imaging.⁴

Neuroblastomas are usually isointense or hypointense to the spinal cord, and there may be areas of necrosis (► Fig. 45.4). On T2-weighted images, neuroblastoma demonstrates some hyperintensity, and there may be areas of hypointensity secondary to calcification, although rarely. After the administration of Gd-DTPA, there is homogeneous or heterogeneous enhancement.⁴² Neurofibromas and schwannomas can be difficult to differentiate; both are isointense on T1-weighted images and hyperintense on T2-weighted images. Schwannomas may have mixed signal intensity on T2 secondary to different cellular populations, Antoni A and B cells.⁴¹ They may hemorrhage and undergo fatty or cystic degeneration, but rarely do they undergo malignant degeneration. Most neurofibromas are in both the intradural extramedullary and extradural compartments, although a small percentage may be totally extradural. They can be single, multiple, or diffuse (► Fig. 45.2). Neurofibromas can demonstrate a central hypointensity, or “target,” on T2, thought to be a dense collection of collagenous stroma. They may also undergo malignant change.⁴¹ Although usually larger and eroding into bone, neurofibrosarcomas may be difficult to differentiate. Areas of necrosis may become evident with contrast. Once an intraspinal lesion is identified, complete neural axis imaging is warranted to examine for intraspinal dissemination or a primary cranial lesion.²

Table 45.5 Initial signs in 504 pediatric patients with intraspinal tumors

Sign	No. of Patients	%
Weakness	351	70
Reflex changes	226	45
Sensory changes	183	36
Curvature	141	28
Atrophy	88	17
Tenderness	62	12
Mass	56	11
Muscle spasm	55	11
Torticollis	33	6
Hydrocephalus	6	1

Source: Adapted from Raffel C, McComb JG. Spinal cord tumors. In: Weinstein SL, ed. *The Pediatric Spine: Principles and Practice*. New York, NY: Raven Press; 1994:917–930.⁶⁸

45.4.3 Myelography

Myelography with water-soluble contrast has previously been used extensively in the evaluation of intraspinal lesions in children.^{5,6,12,15,43} However, deterioration after a lumbar puncture has been reported in patients with intraspinal neoplasms,³⁸ and the risk for hematoma exists with coagulopathy in pediatric patients with cancer.²⁹ Myelography should be reserved for patients who require an emergent study when MR imaging is not immediately available.

In intradural extramedullary tumors, the cord is displaced, with a filling defect in the contrast column. Epidural lesions displace both the cord and the subarachnoid space. A complete block of contrast material may prevent a determination of the upper extent of the tumor.

45.4.4 Computed Tomography

CT with intrathecal water-soluble contrast is an important adjunct to myelography.^{12,44} Contrast medium may pass around a high-grade block seen on a myelogram, defining the upper extent of the lesion without the need for a second injection of contrast material. CT with intrathecal contrast is more sensitive than myelography alone in detecting drop metastases and lesions in the epidural space.⁴⁵ High-resolution CT with intravenous contrast may demonstrate whether a tumor, such as a paraspinal neuroblastoma, is in the canal. As well, contrast enhancement can identify the involvement of great vessels with large paraspinal masses.

CT is the optimal study for assessing the degree of bone involvement. The neuroforaminal widening, bone erosion, and vertebral body scalloping caused by neurofibromas and schwannomas are evident on CT. This information is critical for surgical planning.

45.4.5 Ultrasonography

Ultrasonography is of little value in detecting intraspinal lesions because bone is impenetrable to sound waves. However,

a primary lesion can be detected in children up to 3 months of age, when the posterior spinal elements remain largely cartilaginous. Ultrasonography is a valuable intraoperative tool.^{46,47} The thecal sac can be scanned before dural opening to delineate the extent of the tumor. In a comparison of preoperative MR imaging with intraoperative ultrasound, it was found that tumors of the cauda equina can migrate rostrally during positioning.⁴⁸

45.5 Operative Technique

The goals of the operative management of extramedullary tumors are to (1) obtain tissue for histologic diagnosis, (2) preserve neurologic function, (3) treat pain, and (4) maintain or restore spinal stability and load-bearing capacity.³³ The histological diagnosis requires a percutaneous CT-guided or an open biopsy. Open procedures are performed when the initial presentation is with spinal cord compression or when the lesion is too small or dangerous to be sampled percutaneously. The location of the tumor, suspected or prior diagnoses, and the presence of metastatic disease from another known source also direct the choice of tissue sampling.

Corticosteroid use in the preoperative management of patients with extramedullary masses compressing the spinal cord is important for preserving neurologic function. However, no studies have compared type of steroid, route of administration, or duration of therapy. High-dose dexamethasone therapy is most commonly used until the spinal cord is decompressed and neurologic symptoms are improving. Preoperative and postoperative care includes deep venous thrombosis prophylaxis and neurogenic bowel and bladder training regimens.

In adults, spinal cord compression from malignancy is most often caused by the epidural extension of a metastatic lesion into the vertebral body. Thus, the mass compressing the cord is anterior to the spinal cord. This finding led Sundaresan and colleagues^{49,50} to recommend an anterior approach to these lesions, with resection of the vertebral body. Epidural compression in children with malignant tumors is usually caused by direct extension of the tumor through the vertebral foramen without significant involvement of the bone.^{5,10,38,51,52} The mass compressing the cord is lateral to the vertebral body and can easily be reached through the posterior approach. Accessing the tumor with a laminectomy, laminotomy, or transpedicular approach is usually preferred. The goal is an optimal decompression with maximal safe resection. A gross total resection of a malignant tumor is rarely accomplished. However, subtotal removal can be done with minimal morbidity and no mortality.²⁹ Postoperative spinal stability may be an issue, depending on the extent of tumor involvement, resection, and radiation therapy. Most malignant tumors are not vascular and can be removed with conventional microsurgical technique. The ultrasonic aspirator (Cavitron Ultrasonic Aspirator, Tyco Healthcare, Mansfield, MA) can help remove larger lesions. If the tumor invades the dura, the involved area may be resected and reconstructed with a dural graft. Somatosensory and motor evoked potentials may be useful in cases in which the tumor involves nerve roots.²

45.5.1 Intradural Extramedullary Tumors

The treatment of intradural extramedullary tumors is primarily surgical. These tumors are usually nerve sheath tumors or benign meningiomas, which are separated from the surrounding tissue by a distinct margin (► Fig. 45.1). This margin allows total excision in almost all patients. Some nerve sheath tumors extend into the extradural space through the neural foramen, and into the paravertebral soft tissue. A second extraspinal resection may be required to remove the remaining tumor. Careful histologic examination is critical in patients with neurofibromatosis because these tumors may contain malignant elements. Asymptomatic intradural neurofibromas in patients with neurofibromatosis can be clinically followed up with serial MR imaging studies. Surgical removal is recommended for patients with cord compression, intractable pain, or radiographic enlargement.

Dermoid tumors of the spinal canal are most often associated with dermal sinus. The treatment of these tumors is surgical, and the operation is best undertaken before any infection has occurred. Scarring induced by infection makes resection more difficult. If meningitis is present when the sinus is discovered, surgery should be delayed until the infection has been treated. The wall of these tumors is made up of epidermis and dermis. They enlarge slowly, filling with desquamated epithelium, sweat, and sebaceous material. The wall of the tumor may be densely adherent to the conus medullaris or the cauda equina roots, and the tumor may tunnel into the cord. Attempts to remove the tumor wall may result in a significant postoperative deficit; thus, debulking should be the approach. The portion not in contact with neural tissue can then be removed, and the remaining adherent portion can be coagulated or treated with a carbon dioxide laser. Spilling of tumor contents into the subarachnoid space should be avoided because sterile meningitis may occur.² Serial MR imaging is required to monitor for recurrence.

45.5.2 Extradural Tumors

In children, most epidural tumors are extensions of malignant paraspinal neoplasms that infiltrate the spinal canal through neural foramina. The treatment options for malignant tumors in the spinal canal are surgical decompression, radiation therapy, and chemotherapy. Asymptomatic patients with a small intracanal tumor burden or with chemo- or radiosensitive histology should be treated nonsurgically. Considerable controversy exists regarding the best management of intraspinal tumors producing neurologic deficits. Tumor type, extent of spinal cord compression, and deterioration during radiation or chemotherapy all play a role in the management decisions for patients with these tumors. The location, extent of tumor, and previous radiation also play a role in the surgical approach.

45.6 Treatment Alternatives

The multidisciplinary management of children with primary or metastatic spinal neoplasms has become the mainstay of treatment with surgical decompression/maximal resection,

chemotherapy, and/or radiation. Consultations with radiation and medical oncology are necessary to determine a treatment plan, during which chemotherapy protocols and prior treatment are considered and treatment goals are clarified. Pediatric anesthesia, critical care, and rehabilitation are adjuncts available at pediatric cancer centers providing a holistic treatment approach. Treatment plans are affected by the type of tumor, extent of spinal cord compression, and whether a diagnosis has been established. These factors are examined in the next sections with respect to the two most common intraspinal malignant tumors—neuroblastoma and sarcoma. The degree to which surgery, chemotherapy, and radiation play a role in treatment with respect to overall survival and best neurologic outcome has been studied in several clinical trials.

45.6.1 Outcomes

Neuroblastoma

Treatment options for patients with neuroblastoma and spinal involvement include chemotherapy alone, chemotherapy followed by surgical resection of residual radiographic disease, and surgical resection followed by chemotherapy and radiation therapy. In an early series, nine patients with neuroblastoma and evidence of spinal cord compression underwent chemotherapy alone and had successful elimination of tumor bulk, and all patients were able to walk at the completion of treatment.⁵³ In another study treating patients who had dumbbell neuroblastomas initially with chemotherapy, Plantaz et al showed a reduction in the size of the intraspinal mass in 58% and improvement of neurologic deficits in 92%.⁵⁴ Surgical decompression was avoided in 60% of patients. In a series of 112 patients with epidural compression of the spinal cord, Klein et al²⁸ emphasized that the type of tumor is important in the efficacy of nonsurgical therapy. Spinal cord compression from neuroblastoma developed in 32 of their patients; 12 underwent surgical decompression, 16 received only medical treatment, and 3 were not treated because the compression appeared at the end-stage of the disease. No significant difference was seen in the functional outcomes of patients treated surgically or medically. The combined results of the patients with so-called small cell tumors (neuroblastoma, germ cell tumors, and lymphomas) were similar to those for patients with neuroblastoma. Patients without severe spinal cord compression can be treated successfully without surgical decompression. These results have led to the conclusion that surgery is not indicated for asymptomatic children with intraspinal neuroblastoma and other small cell tumors. Massad and associates³⁸ evaluated 80 patients with neuroblastoma admitted to the Beirut Medical Center over a 21-year period. Twelve of these patients had intraspinal involvement sometime during the course of their disease. Intraspinal disease was more common in those patients with mediastinal versus retroperitoneal disease. Only 5% of the 80 patients presented with spinal cord compression, and none had disseminated disease. Patients with intraspinal involvement and less disseminated disease had better survival at 5 years (50% vs. 21%). The factors that affected survival in this study were age, histologic differentiation of the tumor, duration of neurologic symptoms, and mode of therapy.

Prognosis and surgical outcome may also depend on the International Neuroblastoma Staging System (INSS) stage. In a study from Memorial Sloan-Kettering Cancer Center in New York City,⁵⁵ 46 patients with epidural or neural foramina neuroblastoma were stratified retrospectively into high- and low-risk groups according to INSS stage (high risk, 4; n=31; low risk, <4). Patients with normal neurologic examinations regardless of INSS stage had a low risk for neurologic deterioration following surgery or chemotherapy. Patients with high-grade spinal cord compression and neurologic deficits can respond to chemotherapy, but 25% will worsen and may require an operation for progressive neurologic deficits. Chemotherapy may be avoided in low-risk patients who respond to surgery alone. A significant number of patients who underwent operations (30%) developed spinal deformities postoperatively. Most of the operations (34%) were posterior approaches in the lumbar or thoracic segments without instrumentation. Median survival was not significantly different between high-risk patients who did or did not have high-grade spinal cord compression and between patients whose initial treatment was chemotherapy or surgery. This was consistent with the findings in the low-grade groups. There was a trend toward longer survival in the patients without neurologic deficits (5.2 vs. 2.7 years), but it was not statistically significant ($p=0.07$) and may have been due to lower statistical power.

Sarcoma

The experience of Klein et al²⁸ also suggests that some tumors are better treated with surgical resection. In their series of 29 patients with Ewing sarcoma, 20 underwent surgical decompression and 9 were treated medically. The patients in each group were comparable with respect to their neurologic status. Seven of the surgical patients were able to walk independently when they first came for treatment, and all maintained this functional level after treatment. Of the 13 patients who underwent surgery but were not able to walk, all but 1 improved, and 11 were able to walk independently after treatment. Of the 9 patients treated medically, only 3 were able to walk after undergoing treatment. Likewise, of the 14 patients in this series who had rhabdomyosarcoma, all 5 who underwent surgical decompression were able to walk independently afterward. Of the 9 patients treated medically, 1 remained the same and 1 got worse. This series suggests that surgical decompression is the initial treatment of choice for children with sarcomas and compression of the spinal cord.

The degree of compression noted on initial imaging studies may affect outcomes.⁵⁶ The 33 patients in one series had complete or nearly complete blockage on myelography, or the tumor occupied more than 50% of the spinal canal on MR imaging. Twenty-six patients underwent surgical decompression followed by radiation and chemotherapy. At the time of follow-up, 18 of these patients showed neurologic improvement, 7 were unchanged, and 1 was worse. The other 7 patients underwent treatment with radiation and chemotherapy alone. Among these patients, 1 improved and 4 deteriorated while receiving chemotherapy. Surgical outcomes were superior to medical therapy outcomes in an assessment of bowel and bladder function after treatment. This was confirmed in a subgroup of patients from St. Jude Children's Research Hospital who had complete motor and sensory level deficits, recognized

regardless of tumor type.²⁸ In patients who present with cord compression as the first sign of malignancy, surgery is required for diagnosis regardless of the degree of cord compression or tumor type. Surgical therapy is also required in those patients whose condition deteriorates during medical therapy.

Surgical decompression is indicated for patients with severe compression of the spinal cord regardless of tumor type, symptomatic patients with sarcomas, patients with symptomatic compression who have no diagnosis, and patients whose neurologic function deteriorates during nonsurgical therapy. Others can be treated primarily with chemotherapy and radiation therapy.

45.6.2 Complications

Immediate complications of surgical decompression of the spinal cord are rare. These are most commonly postoperative hematomas and wound complications (infection, dehiscence, and CSF fistulas). Reduction of morbidity and mortality in these cases requires careful preoperative planning. Proper positioning of the patient minimizes pressure sores and reduces ventilatory and venous pressures during extensive operations. Anemia from acute blood loss is a common complication, and the preparation of blood products for perioperative transfusion is essential. Maintenance of normothermia lessens the risk for coagulopathy and metabolic acidosis. In the surgical approaches to patients with extradural and intradural extramedullary spinal masses, consideration of en bloc resection is sometimes required for maximal oncologic treatment. This often involves the collaboration of pediatric thoracic and abdominal surgeons to allow a larger surgical field for more complete removal and the placement of stabilizing instrumentation.

Short-term and delayed spinal deformity may occur as a consequence of posterior decompression with laminectomy, with rates varying from 16 to 100% of cases in children, versus 10% of cases in adults.⁵⁷ In an early series of patients with intraspinal tumors treated with laminectomy, cervical kyphosis, anterior subluxation, and disabling scoliosis were observed.^{58,59} Causes of instability may be vertebral erosion, paraspinous denervation or fibrosis, asymmetric irradiation of the spine, or postsurgical destabilization.⁶⁰ This may also be related to a wedging change in the cartilaginous portion of the vertebral body and to the viscoelasticity of ligaments in children.⁶¹ In one series of 31 patients treated for intraspinal tumors, 7 developed a spinal deformity after laminectomy.¹² The incidence of deformity after multilevel laminectomy is related to the patient's age and the spinal level of the laminectomy (► Table 45.6). Reports from the Children's Memorial Hospital, Chicago, Illinois,⁶² suggest that laminotomy is less likely to cause a deformity than laminectomy.^{12,62} After laminectomy, 39% of patients have shown abnormal curvature, whereas 27% have done so after laminotomy. Using a high-speed pneumatic drill, Abbott et al encountered only one technical complication in 180 laminotomies.⁶³ However, other authors have not been convinced of the superiority of the laminotomy.^{55,64} Laminoplasty has also been associated with a high incidence of postoperative deformity; McGirt and colleagues reported similar risks for deformity with laminoplasty and laminectomy after 20 months postoperatively. Laminoplasty has, however, been associated with a reduction in incisional spinal fluid leaks and reduced hospital stay, but further

Table 45.6 Incidence of spinal deformity after multilevel laminectomy in 58 patients

Characteristic	Percentage of patients with subsequent deformity (%)
Age	
Younger than 15	46
Older than 15	6
Site of laminectomy	
Cervical	100
Thoracic	36
Lumbar	0

Source: Yasuoka S, Peterson HA, MacCarty CS. Incidence of spinal column deformity after multilevel laminectomy in children and adults. *J Neurosurg* 1982;57(4):441–445.⁶⁹

studies in pediatric populations are required to determine if this association is significant.⁵⁷

One series of 255 children with intramedullary spinal tumors compared the occurrence of postlaminectomy spinal deformity in children who underwent decompression and fusion at the time of surgery with the occurrence of deformity in those who underwent decompression alone. Moderate and severe deformity, defined as scoliosis of more than 25 degrees and/or sagittal imbalance of more than 20 degrees requiring bracing or surgery, developed in 21 of 37 resections (57%) without fusion and in 4 of 15 resections (27%) with fusion. Laminectomy involving laminae at more than three levels demonstrated a significant association with postoperative deformity. Although this series includes only intramedullary tumors, it raises the question of considering postoperative outcomes when a surgical plan is made. For younger patients who have undergone cervical decompression with a multilevel laminectomy, immobilization with a cervical collar is recommended for 3 to 6 months. The first-line treatment for many children with spinal tumors will be a posterior decompression with resection; these patients must be followed closely to monitor for postoperative deformity.⁶⁵

Spinal deformity is also a complication of radiation therapy. Mayfield and colleagues⁶⁰ reported that significant spinal deformities developed in 32 of 57 patients (56%) with neuroblastoma treated with radiation therapy and chemotherapy. A rate as high as 71% has been reported.⁶⁶ A higher rate of deformity is associated with younger age at the time of radiation, doses greater than 20 Gy, and asymmetric radiation fields.^{60,66,67} Radiation-induced myelopathy occurs more frequently at the midthoracic region, the watershed area of the spinal cord. The degree of injury varies with total radiation dose, fraction size, and length and duration of treatment. A threshold for radiotherapy of 45 to 50 Gy has been suggested, delivered in fractions of 1.8 to 2 Gy. With image guidance systems, radiosurgical methods can now be applied to extracranial targets. Mainly used in adult patients with spinal metastases, the concern for posttreatment deformity and radiation-induced myelopathy persists. Further studies are needed to examine the impact on the pediatric population.³⁰

The combination of laminectomy and radiation can pose severe risk for the development of spinal deformity.^{60,66,67} In children who have an epidural tumor without evident cord

compression or neurologic deficit, both surgery and radiation therapy should be avoided. If possible, a child with an epidural tumor should undergo chemotherapy alone. For those patients who require surgery, consideration should be given to bone grafting and/or implants with instrumentation if the degree of tumor or bone removal may result in spinal instability.

Pearls

- CNS tumors are responsible for 24% of cancer-related pediatric fatalities, and 5 to 10% of these tumors arise in the spinal axis.
- In patients with extramedullary spinal tumors, weakness and pain are the most common presenting symptoms.
- Cord compression develops in 3 to 5% of children with a systemic cancer.
- The mass compressing the cord is lateral to the vertebral body and can easily be reached through the posterior approach.
- The multidisciplinary management of children with primary or metastatic spinal neoplasms has become the mainstay of treatment with surgical decompression/maximal resection, chemotherapy, and/or radiation.
- The first-line treatment for many children with spinal tumors will be a posterior decompression with resection; these patients must be followed closely to monitor for postoperative deformity.

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46 Intramedullary Spinal Cord Tumors

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Primary spinal cord tumors account for approximately 2 to 4% of all central nervous system neoplasms.¹⁻³ The percentage approaches 35% in the pediatric population as well as in young adults,¹ and roughly 100 to 150 cases of pediatric intramedullary spinal cord tumors (IMSCTs) are diagnosed in the United States each year.¹ Ependymomas, astrocytomas, and gangliogliomas account for approximately 80% of IMSCTs.⁴⁻⁸

The development of modern microsurgical techniques, operative equipment, neuroimaging, and intraoperative neurophysiology has elevated aggressive resection of these lesions to the standard of care.^{1,5,6,9,10} As a result, these patients have experienced improvement in long-term survival and quality of life, although late recurrences do occur despite adequate surgical resection. Adjuvant therapy, including radiation and chemotherapy, has resulted in only modest improvement in survival. Tumor location, the patient's age, pathology, and the ability to achieve a gross total resection (GTR) determine whether any adjuvant treatment is necessary.

46.1 Epidemiology

IMSCTs are found throughout the entire neuraxis. In the pediatric population, the majority of these lesions occur in the cervical and cervicothoracic region,^{7,8,11,12} whereas in adults the incidence of intradural extramedullary tumors is increased, and thus the number of lumbar lesions that are diagnosed.⁵ Astrocytomas are the most common IMSCTs found in children^{5,6} but can occur at any age.^{2,7,13} In patients younger than 10 years of age, more than 90% of spinal cord tumors are glial in origin, although this percentage declines to 60% of patients by the adolescent years,^{5,12} with an increased prevalence of ependymomas.

Ependymomas are believed to arise from the ependymal lining of the ventricles and central canal in the brain and spinal cord. There is an association with neurofibromatosis, but most cases are spontaneous. In children, ependymomas are the second most common lesion following astrocytomas and typically occur in the cervical region.^{5,13-15} In children, more than 90% of the tumors are intracranial in origin, and in one series no spinal cord ependymomas were diagnosed in children younger than 3 years of age.¹⁶

46.1.1 Associations with Neurofibromatosis

Neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2) are both associated with tumors of the central nervous

system.¹⁷ NF-1 is an autosomal-dominant disorder with complete penetrance. It has a prevalence of 1 per 3,000. NF-2 is a rarer disease, with a prevalence of 1 per 40,000 people.¹⁸ It is caused by a mutation of the tumor suppressor gene on chromosome 22 called merlin or schwannomin.⁵

Dow and colleagues showed that patients with NF-1 were more likely to present with IMSCTs that were astrocytomas, whereas patients with NF-2 more commonly had IMSCTs that were ependymomas.¹⁹ In the series of Lee and colleagues, the incidence of IMSCT in the total population of patients with neurofibromatosis was 19%.¹⁸ In the series of Malis et al, among 41 patients with NF-2 and 99 spinal tumors, 14 presented with intramedullary tumors.²⁰ NF-2 is more commonly associated with schwannomas and meningiomas, but there is also an association with IMSCTs. Although patients with NF-2 comprise only 0.03% of the population, they are overrepresented among patients who have IMSCTs (2.5%).¹⁸ Additionally, Birch and colleagues showed that 71% of patients with intramedullary ependymomas who did not meet the clinical criteria for NF had mutations in the *NF2* gene²¹ (► Table 46.1).

46.2 Presentation

As in patients with other neuraxis lesions, symptoms depend on the location of the tumor. Most commonly, patients present with pain, followed by gait deterioration, weakness, bowel and/or bladder dysfunction, and sensory disturbance.^{6,10,15} Sensory changes also present differently across the age groups. In young children, localization can be difficult. Their symptoms may manifest only through general irritability or an avoidance of certain positions. Older children sometimes describe a dull, aching, nonspecific type of nocturnal pain. Adolescents may attribute their pain to normal growth and may not present until they demonstrate weakness or an atypical focal finding, such as a subtle change in gait or frequent falling. The pain is typically worse in the supine position as venous congestion distends the dura, causing nocturnal pain. Adults, conversely, will recognize a deterioration of normal function and present with a more classic sensory disturbance.^{15,22}

Children also manifest other typical findings differently from adults. Weakness may be difficult to detect in young children, who are innately clumsy as they are learning to walk. Bowel and bladder dysfunction may also be difficult to detect in infants who are not toilet-trained. However, in a child who has

Table 46.1 Clinical manifestations of neurofibromatosis type 1 and type 2 and associated intramedullary spinal cord tumors

	Neurofibromatosis type 1	Neurofibromatosis type 2
Genetic mutations	von Recklinghausen	merlin, schwannomin
	Chromosome 17	Chromosome 22
Associated intramedullary spinal cord tumors	Astrocytoma	Ependymoma
Other associated central nervous system tumors	Nerve root neurofibromas, optic nerve gliomas, meningiomas	Bilateral acoustic neuromas and schwannomas

Table 46.2 Magnetic resonance imaging characteristics of intramedullary astrocytomas and ependymomas

	Astrocytomas	Ependymomas
Location	Eccentric location Cervicothoracic spine Can extend holocord	Central location Cervical spine
T1	Iso- to hypointense	Iso- to hypointense
T1 with contrast	Heterogeneous contrast enhancement with ill-defined borders	Symmetric contrast enhancement with sharply defined borders
T2	Hyperintense	Hyperintense
Cysts	Less common than with ependymomas except for juvenile pilocytic astrocytomas	Three types of cysts: tumoral cysts from necrosis and hemorrhage, syrinx formation, rostral and caudal cysts from reactive tumor products
Unique findings	Peritumoral edema, more commonly associated with syrinx formation	“Cap” sign, in which areas of low signal density appear on either tumor border that are due to hemosiderin deposits from secondary, chronic hemorrhage

been previously toilet-trained, loss of bowel and bladder control can be a manifestation of an underlying pathology.^{6,10}

Ependymomas, arising from the ependymal cells of the central canal, are well-circumscribed, slow-growing tumors that are centrally located and cause symmetric expansion of the spinal cord.^{5, 23,24} Patients typically present with bilateral dysesthesias at the level of the tumor, as well as paresthesias, radicular pain, bowel and bladder dysfunction, and other sensory disturbances.^{15,22,24} Children commonly present with pain, weakness, gait abnormality, torticollis, or progressive kyphoscoliosis.^{1,6} Hydrocephalus is more commonly found in pediatric patients with spinal cord ependymomas or myxopapillary ependymomas than in those with other IMSCTs and requires shunting occasionally. However, hydrocephalus develops in fewer than 10% of patients, and the etiology is an increased protein content in the cerebrospinal fluid (CSF), arachnoidal fibrosis, and subarachnoid metastasis.^{10,25} Acute decline can follow an intratumoral hemorrhage.²⁴

Patients with IMSCT astrocytomas have symptoms similar to those of patients with ependymomas. Worsening of motor symptoms tends to be earlier in the disease process in these patients than in those with ependymomas. Spinal deformity can be common and presents in up to 30% of patients.^{2,26} High cervical lesions with involvement of the medulla can present with bulbar symptoms, including vomiting, choking, dysphagia, frequent respiratory infections secondary to chronic aspiration, dysarthria, dysphonic speech, and sleep apnea. In younger children, these deficits can manifest as failure to thrive.

46.3 Imaging Characteristics

Magnetic resonance (MR) imaging has dramatically changed the way IMSCTs are evaluated because this is typically the only imaging modality needed to establish the diagnosis. Intramedullary lesions appear as an area of cord expansion on MR imaging and are often associated with cysts or syringomyelia. Tumors may appear isodense on T1-weighted images, and tumoral cysts are hyperintense on T2-weighted images because of the high protein content. The majority of tumors will enhance after gadolinium administration, and differences in enhancement may suggest certain histologies.²⁷ Although a precise histologic diagnosis is not possible via imaging, the lesions do tend to follow typical patterns on imaging²⁷⁻²⁹ (► Table 46.2).

46.4 Differential Diagnosis

Overall, the most common lesions are primary glial tumors. Astrocytomas are the most commonly occurring lesion, followed closely by ependymomas, gangliogliomas, oligodendrogliomas, neurodevelopmental tumors, and malignant gliomas.⁵ Other, nonneoplastic lesions may also occur, such as cavernous malformations and arteriovenous malformations, as well as infectious and inflammatory pathologies.

46.4.1 Astrocytomas

IMSCT astrocytomas arise from transformed astrocytes that then infiltrate the spinal cord. They are histologically identical to intracranial astrocytomas and are graded on the same World Health Organization (WHO) scale: pilocytic lesions (grade I), low-grade astrocytomas (grade II), anaplastic astrocytomas (grade III), and glioblastoma multiforme (grade IV).

Astrocytomas are the most common IMSCTs occurring in children and account for nearly 40 to 60% of lesions.^{1,6,10,15,22} They are the second most common type in adults, with a frequency of 20 to 30%.^{2,5} (► Fig. 46.1). Compared with their intracranial counterparts, they are more benign in presentation and are more commonly low-grade lesions at diagnosis. High-grade astrocytomas comprise 10 to 15% of pediatric spinal cord tumors.^{2,5} They more commonly occur in the cervical and thoracic region in children (► Fig. 46.2). Juvenile pilocytic astrocytomas may be associated with large tumoral cysts; the solid component is often well localized and should be the area that is targeted surgically.^{9,22}

Although genetic alterations are well described for intracranial tumors, very few data exist for spinal cord lesions. However, we assume that there is a correlation because some IMSCT astrocytomas are clustered with inherited syndromes: Li-Fraumeni syndrome, Turcot syndrome, tuberous sclerosis, Maffucci-Ollier disease, and NF.⁵ Although less common than in adult tumors, chromosomal changes in 7, 22, and 10 and molecular alterations of *EGFR*, *PTEN*, and *IDH1* have all been identified in a subset of pediatric gliomas and may contribute to the transition from low-grade to high-grade astrocytoma.^{12,30} However, the genomic changes in most pediatric astrocytomas differ from those in

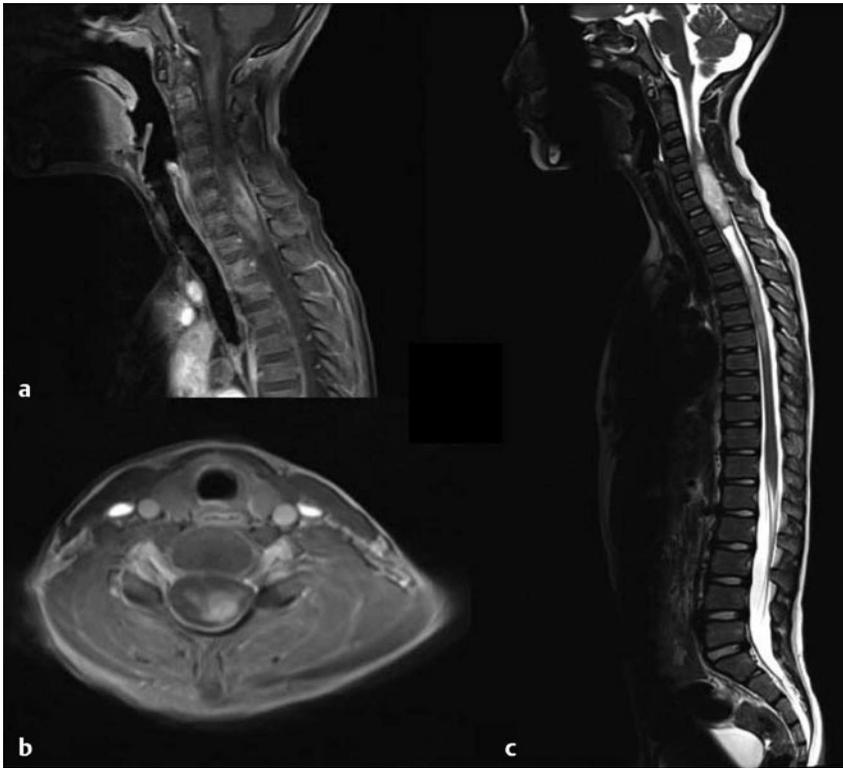


Fig. 46.1 Magnetic resonance imaging in a patient presenting with progressive myelopathy over many months. The histologic diagnosis was World Health Organization grade I astrocytoma. (a) Sagittal T1-weighted image demonstrating heterogeneous enhancement with expansion of the spinal cord. (b) Axial T1-weighted image showing contrast enhancement eccentrically located within the spinal cord. (c) Sagittal T2-weighted axial image showing diffuse hyperintensity with caudal syrinx formation.

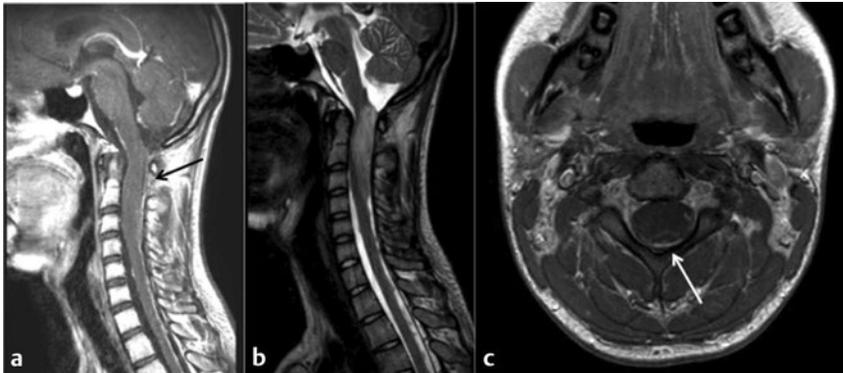


Fig. 46.2 Magnetic resonance imaging in a patient presenting with the acute onset of difficulty walking. The histologic diagnosis was World Health Organization grade IV astrocytoma. (a) Sagittal T1-weighted image shows minimal enhancement of the tumor itself, with the *black arrow* indicating diffuse pial enhancement. (b) Sagittal T2-weighted image showing hyperintensity and edema throughout the cervicomedullary junction. (c) Axial T1-weighted image, with the *white arrow* showing contrast enhancement along the pial border.

adults, suggesting that these tumors may arise from different molecular pathways, which is an area of intense investigation.

46.4.2 Ependymomas

Ependymomas account for 4 to 6% of primary central nervous system tumors, with approximately 30% of these lesions being intraspinal.^{5,12} They can be divided into four subtypes via the WHO classification: subependymoma, myxopapillary ependymoma (grade I), benign or “classic” ependymoma (grade II), and anaplastic ependymoma (grade III). Subependymomas rarely occur in the spinal cord and are mostly intraventricular. Myxopapillary lesions arise from the filum terminale or conus medullaris and are thus found in the lumbar region 20 to 25% of the time, most commonly in adults.¹² Most benign and anaplastic lesions occur in the cervical region. They tend to present in adults between the ages of 30 and 50 years but are the second most com-

mon lesion in the pediatric population (► Fig. 46.3). These tumors are relatively avascular but typically receive their blood supply from branches of the anterior spinal artery, and care should be taken to preserve the normal vasculature during removal.

Approximately 75% of all ependymomas have some chromosomal rearrangement or change.⁵ Mutations of the genes on chromosome 22 associated with NF-2 (merlin) are the most common and occur about 40% of the time. Other chromosomes that have been implicated are chromosome 6 (30.3% of the time), chromosome 9 (27.3% of the time), and chromosome 17^{12,18,19}. The molecular and genetic events that distinguish spinal ependymomas from intracranial ependymomas are more defined than those for spinal and intracranial astrocytomas. Methylation patterns in certain genes, including the tumor suppressor gene *HIC1*, have been implicated in intracranial lesions compared with spinal ependymomas.^{5,12,30} Most recently, Johnson and colleagues have shown distinct genetic signatures for

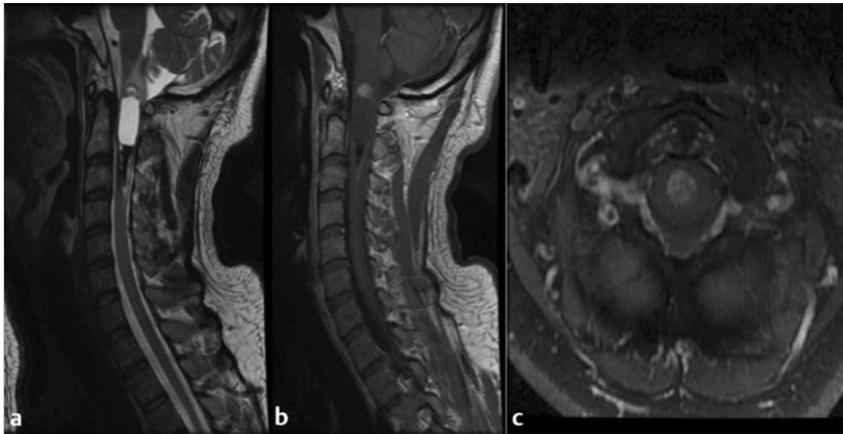


Fig. 46.3 Magnetic resonance imaging in a patient presenting with neck pain over a period of several years who was originally followed conservatively and showed progression. The histologic diagnosis was ependymoma. (a) Sagittal T2-weighted image showing hyperintensity in a central location. Both rostral and caudal cysts show evidence of prior hemorrhage and the classic “cap” sign. (b) Sagittal T1-weighted image shows minimal enhancement of the tumor. (c) Axial T1-weighted image showing central heterogeneous enhancement.

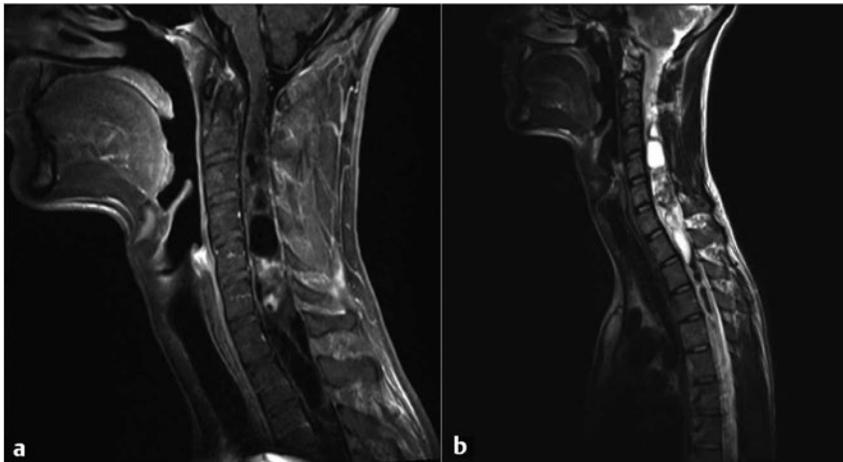


Fig. 46.4 Magnetic resonance imaging in a patient presenting with myelopathy over several years. The histologic diagnosis was ganglioglioma. (a) Sagittal T1-weighted image demonstrating heterogeneous nodular enhancement. (b) Sagittal T2-weighted image demonstrating extensive cystic components both rostral and caudal to the nodular area.

intracranial ependymomas compared with ependymomas originating in the spinal cord. Members of the Notch and Sonic Hedgehog pathways are overexpressed in intracranial ependymomas, whereas overexpression of the Homeobox-containing family of genes (*HOX*) is implicated in spinal cord ependymomas.³¹ These authors have also found that ependymomas are derived from regionally specific stem cells bearing a radial glial cell phenotype.³¹

46.4.3 Gangliogliomas

Gangliogliomas are composed of both neuronal and glial cells. The glial elements are typically astrocytes, and the neoplastic neurons are large and mature in appearance. The frequency of these tumors among IMSCTs has been reported to be as high as 27% in some series,^{11,32} and lesions can be infiltrative (► Fig. 46.4). They are slow-growing and occur in the cervical and upper thoracic spine in an eccentric location. Given their slow growth, they can be associated with bony erosion or scalloping. On imaging, they have areas of mixed signal on T1-weighted images, with heterogeneous enhancement that extends to the surface of the spinal cord, and are associated with prominent tumoral cysts.^{11,32}

46.4.4 Lipomas

Lipomas account for 1% of IMSCTs and arise from embryonal clefts. Although they are commonly thought to be associated with spinal dysraphism, they are indolent in nature, and the presentation is often delayed until adulthood. They are commonly located in the thoracic spinal cord¹² and are histologically identical to normal adipose tissue. They may grow, like any other fatty deposit in the body, and patients may manifest myelopathic signs following spurts of growth or weight gain. Lipomas typically appear as hyperintense lesions on T1-weighted imaging without contrast. Although these lesions are distinct from the spinal cord, they are densely adherent, so that total removal without neurologic deficits is difficult.²⁷

46.4.5 Hemangioblastomas

Hemangioblastomas are relatively rare in the pediatric population, but if found, they are typically associated with von Hippel-Lindau disease.^{5,33} They are located on the dorsal surface of the spinal cord and are associated with large feeding and draining vessels.

46.4.6 Others

Lymphomas and metastatic lesions are more common in the adult population. Lymphomas are rare and are associated with AIDS. They are almost uniformly found in adults. Vascular malformations, including cavernous angiomas, are similar to their intracranial counterparts. They typically present in young adulthood, either with multiple small hemorrhages leading to myelopathy or with an acute hemorrhage that leads to an acute neurologic decline.¹² They account for 1 to 3% of all IMSCTs. Metastatic lesions are also almost always found in adults and can occur from both hematogenous spread and direct leptomeningeal invasion.¹² Other IMSCTs include dermoids, teratomas, oligodendrogliomas, and nonneoplastic lesions, such as sarcooid and multiple sclerosis.

Other intramedullary spinal lesions include inclusion tumors and cysts, nerve sheath tumors, neurocytomas, and melanocytomas. Approximately 4% of IMSCT are found to be non-neoplastic lesions.^{5,12}

46.5 Treatment Strategy

Surgical intervention is the primary treatment of choice for IMSCTs; the goal is complete resection because progression-free survival (PFS) is good when this occurs.^{8,11,13,14,24} Despite multiple trials and retrospective reports, little progress has been made with adjuvant therapy to improve overall survival (OS). Radiation treatment is more widely accepted for patients with incomplete resection and for those with astrocytomas. The clinical benefits of GTR are best established for ependymomas.

The natural history of many IMSCTs is more benign than that of their intracranial counterparts. These patients are often neurologically stable for years with simple observation. However, most surgeons agree that open surgery is indicated because the lesions undoubtedly eventually progress to neurologic deficit.^{5,10,12,22} The outcome for low-grade spinal cord astrocytomas is better in children than in adults, although the prognosis for astrocytoma is not as favorable as that for ependymoma.^{8,10,23,34} Several series have shown that patients with good preoperative function have a better recovery following operation than those with more severe preoperative symptoms.^{7,8,15} One hypothesis is that the spinal cord tissue is more plastic in children than in adults, and this portends a better prognosis.

46.5.1 Surgery

The goal of surgery for low-grade IMSCTs remains GTR with preservation of neurologic function.^{3,8,9} Although the data are more controversial for astrocytomas, several series with data for grade II and grade III lesions have demonstrated an improvement in OS and PFS with aggressive resection of the tumor.^{3,8,22} There are no class I studies for the treatment of IMSCTs.

Maintaining the patient's neurologic function remains an important goal of surgery. Patients with minimal preoperative symptoms have a greater potential for improvement postoperatively. If the tumor is infiltrative, then decompression of the

adjacent spinal cord and the avoidance of neurologic dysfunction should be the goal.^{1,12,23} Closely adherent tumor should not be forcibly removed.⁶ Surgery should ideally occur before the patient has experienced a major neurologic decline because the potential to stabilize or to regain function is limited in these patients.

Astrocytomas are typically eccentrically located several millimeters beneath the dorsal surface of the spinal cord. Radical resection is more controversial because they are infiltrative in nature. However, an excellent prognosis has been reported for patients with low-grade astrocytomas,^{2,7,22} and a radical resection will improve PFS and OS for these patients. These tumors harbor microscopic disease beyond what is visible at the time of surgery, and thus the removal of all cellular atypia is unlikely. Therefore, resection should be continued until the interface between normal spinal cord and tumor tissue becomes difficult to differentiate, so as to minimize the resection of normal neurologic pathways.^{6,8} The tumors are typically resected from the inside out until the glia-tumor interface is identified by the change in color and consistency of adjacent spinal cord. Neuro evoked potentials are critical to guide the extent of resection in the event that motor pathways impede resection.

Like intracranial lesions, high-grade astrocytomas have a poor prognosis, which is not altered by surgical resection.^{1,7,22} Despite resection, they recur rapidly and metastasize throughout the subarachnoid space within a few months. An early biopsy should be taken during surgery if there is any concern for atypia because this will influence how aggressively the tumor will be removed. Evidence of a high-grade lesion, such as a glioblastoma, portends a poor prognosis despite surgical resection. In this case, if there is a cystic component that is causing mass effect, then decompression may lead to some temporary relief of symptoms. However, the patients do poorly and have a median survival of less than 2 years even with adjuvant therapy.

Ependymomas are more distinct from the surrounding spinal cord and have a clear cleavage plane that facilitates resection.¹⁴ They are central in location, and given their cystic nature, the cleavage plane can be further defined at the poles of the tumor. The goal at surgery is to minimize trauma and traction on the normal spinal cord.^{6,9,14} Because PFS correlates with the extent of resection, the surgeon should pursue a GTR.^{5,12,22} However, if the interface between tumor and normal spinal cord becomes indiscernible, then the resection should be halted because neurologic function should be preserved.

46.5.2 Intraoperative Management

Surgical technique is determined by the tumor size and histologic diagnosis at the time of biopsy. A laminoplasty can be performed to expose the extent of the solid component of tumor.⁷ Although laminoplasty has not been definitively shown to reduce the progression of deformity, it has been shown to lower the CSF leakage rate and to help preserve normal anatomical planes.³⁵ If there is concern for the accuracy of the surgical exposure and identification of the tumor, intraoperative ultrasound may be obtained to optimize the size of the laminoplasty, dural opening, and myelotomy. Ultrasonography can also be an important adjunct for identifying the solid and cystic components of the tumor and for determining the depth of resection.

Intraoperative electrophysiologic monitoring is critical to establish the extent of resection during removal of an IMSCT. Somatosensory evoked potentials (SSEPs) measure the afferent conduction of impulses from a peripheral nerve to the brainstem or cerebral cortex. Degradation of the signal results from insult to the sensory pathways, such as the dorsal columns or anterolateral tracts.^{36,37} SSEPs are recorded as an average of many signals, and this can delay the detection of injury. Therefore, motor evoked potentials (MEPs) and epidural electrodes give a better real-time estimate of the integrity of motor pathways. MEPs record a peripheral response to cortical stimulation and are shown as an “all-or-none” interpretation profile. The epidural MEP, or D-wave, measures the direct activation of large-diameter corticospinal axons through stimulation of the spinal cord with an electric current. The amplitude of this signal correlates with the number of intact descending motor units or functioning axons.^{36–38} The epidural electrodes are placed both rostral and caudal to the tumor following the laminectomy.

The intraoperative monitoring of D-waves can make it possible to predict the postoperative functional outcome of patients.³⁸ Both MEP and D-wave monitoring can predict spinal cord damage and transient postoperative effects. If the muscle MEPs are lost but the D-wave is preserved during surgery, then the patient typically has a transient deficit postoperatively. A decrement of 50% in the amplitude of MEPs is an indication to halt surgical resection because this is a measure of a temporary as well as a potentially permanent deficit^{8,36–38} (► Table 46.3). These techniques rely on computer averaging, so there can be a brief delay of 10 to 60 seconds between the time of injury and visualization of a declining response amplitude.

This technology is not without limitations because intraoperative mapping can be influenced by other factors. Anesthetic agents can affect whether nerves can be mapped. Close discussion with the anesthesiologists should be conducted to minimize the intermittent administration of boluses of intravenous anesthetics and of halogenated anesthetics, and to avoid hypothermia. Paralytic agents should also be avoided because they can influence the ability to record MEPs. If the patient has significant weakness preoperatively, the signals can be difficult to obtain and follow.

46.5.3 Deformity

Spinal deformity occurs in conjunction with IMSCTs even if there are no neurologic signs or symptoms. Some children can even present with scoliosis, and up to 37% of children will require stabilization or a brace.¹⁴ This high rate of instability relates to the relative laxity of the ligaments, the horizontal orientation of facet joints, and the dynamic growth of the

osseous spine.^{14,39} Given the low prevalence of instability, prophylactic instrumentation is not used. However, several risk factors are associated with progression to fusion, included age younger than 13 years, involvement of the thoracolumbar junction, tumor-associated syrinx, and preoperative scoliotic deformity^{1,6,7,26} (see box “Predictors of Progressive Spinal Deformity Requiring Fusion after Resection of Intramedullary Spinal Cord Tumors (p.610)”). The incidence of progressive kyphoscoliosis in the thoracic spine and swan neck deformities in the cervical spine is higher in children than in adults.^{7,26} The cervical region is more prone to destabilization than the thoracic or lumbar region. Deformity is also related to the extent of the bony decompression. Radiation and tumor-induced paraspinal muscular weakness further destabilize the body’s ability to compensate for bony loss.^{26,39}

Predictors of Progressive Spinal Deformity Requiring Fusion after Resection of Intramedullary Spinal Cord Tumors

Predictors of progressive spinal deformity requiring fusion:

- Age younger than 13 years
- Symptoms for less than 1 month
- Preoperative scoliosis
- Thoracolumbar involvement
- Syrinx (on preoperative magnetic resonance imaging)
- Higher total number of operations

Adapted from Yao KC, McGirt MJ, Chaichana KL, Constantini S, Jallo GI. Risk factors for progressive spinal deformity following resection of intramedullary spinal cord tumors in children: an analysis of 161 consecutive cases. *J Neurosurg* 2007;107(6 Suppl):465.⁴⁴

There is controversy regarding the need for spinal fusion at the time of surgery to prevent progressive deformity after IMSCT resection. In a review of 33 patients, Simon et al found that 25% of patients who underwent fusion at the time of tumor resection progressed to significant spinal deformity, compared with 62% of patients who underwent laminectomy and laminoplasty alone.³⁹ External orthotic bracing is also an option to prevent postoperative spinal deformities. However, this is sometimes not comfortable and can lead to social stigma in young children, although it is otherwise well tolerated. We typically recommend preoperative X-rays so that these children can be followed with serial imaging studies.

46.5.4 Radiation

Radiation treatment has been limited to instances of incomplete resection and malignant tumors.⁴⁰ Radiation has

Table 46.3 Interpretation of motor evoked potentials during intramedullary spinal cord resection

D-wave ^a	Muscle motor evoked potential ^b	Postoperative motor status
Decreased <50%	Unchanged	Unchanged
Decreased <50%	Unilateral or bilateral loss	Transient motor deficit
Decreased >50%	Bilateral loss	Prolonged motor deficit

^aD-wave measures the direct activation of large-diameter corticospinal axons through direct stimulation of the spinal cord by an epidural electrode.

^bMuscle motor evoked potentials measure the peripheral response to cortical stimulation as an “all-or-none” interpretation.

deleterious effects on the vertebral column and increases the risk for secondary neoplasms many years later. For this reason, there is growing consensus to delay radiation treatment as long as possible in the pediatric population.¹²

Radiation for low-grade ependymomas remains controversial. Multiple series show that long-term tumor control is better with GTR than with subtotal resection and radiation.^{5,9,12} Most centers do not recommend radiation treatment if GTR is obtained, despite a risk for recurrence of 5 to 10% at 10 years.⁴⁰ For patients in whom a GTR cannot be obtained, postoperative radiation is based on small studies with limited follow-up.⁴⁰ However, most studies show some benefit for radiation following subtotal resection of an ependymoma.⁴⁰ Some centers will advocate reoperation and another attempt at resection at the time of recurrence before radiation.^{23,40}

For astrocytomas, GTR is not often achieved, and radiation is less controversial. Many still advocate monitoring with serial MR imaging and reoperating if there is concern for regrowth and worsening symptoms because the natural history of these lesions is indolent. However, other authors have shown some improvement in survival with adjuvant radiation. Patients with malignant astrocytomas typically undergo total neuraxis radiation and chemotherapy, although this has shown to have limited efficacy in achieving long-term survival.

The typical dose is 5,000 to 5,500 cGy delivered in fractions of 180 to 200 cGy with external beam radiation. The lesion is typically radiated only at the area of focal disease because most recurrences are local and do not disseminate.⁴⁰ For young children, the overall radiation dose is lowered by at least 1,000 cGy because they are more susceptible to the adverse effects of radiation. Craniospinal radiation is rarely warranted for low-grade lesions and is indicated only when there is multifocal disease that is not amenable to GTR.⁴⁰

46.5.5 Chemotherapy

The role of chemotherapy has not been clearly defined in the treatment of IMSCTs. Despite the widespread use of chemotherapy for intracranial lesions, the improvement in outcome for patients with spinal cord lesions has not been as definitive. The guidelines for pediatric IMSCTs have been extrapolated from our clinical experience with intracranial ependymomas and low-grade astrocytomas.⁴¹ No randomized clinical trials have been performed, and most series are limited, with small numbers of intramedullary spinal lesions. However, given the desire to delay or avoid radiation therapy in young children, adjuvant chemotherapy plays a role in delaying radiation.

Multiple drugs have been studied as treatment for supratentorial ependymomas. Platinum-based regimens in conjunction with nitrosourea-based regimens have shown some promise.⁴¹ Etoposide, a topoisomerase II inhibitor, has also been used to treat recurrent intramedullary ependymomas and is apparently well tolerated. Two recent reports of pediatric IMSCT astrocytomas demonstrated adequate results, showing a potential to target these tissues and improve patient survival.⁴¹

46.6 Outcome

Patient outcomes are influenced by three major factors: histologic grade of the tumor, preoperative functional status,

and surgical resection. The histologic grade often correlates with the degree of invasiveness and the possibility to obtain a GTR. Children with low-grade astrocytomas can have a survival of 60 to 80% at 5 years. Children with juvenile pilocytic astrocytomas have a better prognosis than those with diffuse fibrillary astrocytomas.²⁵ Malignant astrocytomas have a poor prognosis despite extensive resection. Most low-grade ependymomas have a high likelihood of being completely resected. Higher-grade ependymomas are scarce among intramedullary spinal lesions. Low-grade astrocytomas are biologically more indolent than their intracranial counterparts in both adults and children.

As discussed previously, surgical resection is an important predictor of outcome and long-term survival for any type of low-grade lesion. OS and PFS in patients with high-grade lesions have not been altered despite aggressive resection. Several series have shown a survival benefit with resection of more than 95% of tumor across all low-grade glial tumors.^{6,15,22} GTR is often more likely to be accomplished for ependymomas than for astrocytomas. Despite GTR, late recurrences can occur, even 12 years following surgery. Local control rates can be 90 to 100% with surgery even if GTR cannot be accomplished. Overall, patients with ependymomas have prolonged PFS and OS, with a median of 82 and 180 months, respectively.^{5,12,14}

Postoperative functional outcome is most strongly tied to preoperative functional ability.^{7,12,23,42} Despite a successful surgical excision, a severe or long-standing preoperative deficit is unlikely to show any improvement.^{5,7} Surgical morbidity is also more significant in those patients with preoperative deficits.^{5,7}

The most common neurologic dysfunction following surgery is dorsal column dysfunction. Despite this difficulty, most patients are able to ambulate independently within a few months.⁷ Other sensory deficits improve over a 3-month period.^{7,22} Additional morbidity is related to the location of the tumor and spinal cord atrophy. Thoracic lesions have been associated with a higher likelihood of decline, perhaps because of a more tenuous blood supply.²³

Age is also associated with the likelihood of postoperative recovery. Postoperative neurologic function was improved or stable in 75 to 90% of adolescent patients.^{7,15,23} These patients also had a faster improvement in neurologic function immediately following surgery than comparable adults did. In younger patients with postoperative deterioration, recovery and normalization were seen as early as 2 to 6 months.⁵ Conversely, adults were more likely to have a prolonged recovery with a higher likelihood of permanent deficits.

46.7 Future Studies

GTR will remain the first-line therapy for low-grade IMSCTs. However, adequate adjuvant therapy has continued to be more elusive for these lesions than for their intracranial counterparts. Despite an indolent course, the lesions do progress and eventually lead to neurologic decline and severe morbidity. Although radiation can provide some symptomatic relief and perhaps a delay in symptoms, it may not produce a definitive halt in disease progression. Future therapies will likely concentrate on targeting complementary or synergistic antitumoral agents at these low-grade lesions. Chemotherapy does not play a role in OS, likely because the blood-brain barrier interferes with the

access of systemically administered therapies to the spinal cord. These lesions grow slowly, so that conventional chemotherapy and radiation, which target rapid cellular turnover and angiogenesis, may not be the best agents for treating low-grade lesions. As we better understand the genetics and epigenetics that make these IMSCTs unique, we will undoubtedly find better targets for adjuvant therapy. Local delivery within the tumor bed has shown some promise; injection of a gel embedded with chemotherapeutic agents into an IMSCT achieved an improvement in median survival and improved functional motor scores in a murine model.⁴³ However, whether this therapeutic option will have any efficacy in treating human IMSCTs remains to be seen.

46.8 Conclusion

IMSCTs remain challenging lesions, but significant advances have been made over the past several decades. Modern microsurgical advances and the advent of MR imaging have made it possible to classify these lesions and improve OS. In children, IMSCTs are typically low-grade lesions and have an indolent natural history. They are most commonly low-grade astrocytomas, and adjuvant radiation and chemotherapy have not made a significant impact on PFS or OS.

Current standards of care include surgery with GTR for ependymomas and attempted GTR for low-grade astrocytomas. Surgical resection should continue as long as a cleavage plane exists and there is minimal adherence to normal neural tissue. If postoperative MR imaging demonstrates unexpected residual tumor, the patient should undergo a second-look operation to achieve maximum resection. Osteoplastic laminoplasty should be used to decrease postoperative CSF leaks and prevent spinal deformity. If a GTR is achieved, then radiation therapy should be withheld. Current guidelines include holding radiation therapy if radical or total resection of low-grade astrocytomas is achieved. Intraoperative ultrasonography, SSEPs, and MEPs should be used to guide the extent of resection. Patients with malignant astrocytomas should undergo limited resection with postoperative irradiation.

Surgery should be considered first-line therapy for these patients. Neurologic improvement following surgery is unlikely unless the preoperative deficits are due to mass effect from an intratumoral cyst or syrinx. However, across all ages, children have the best potential for improvement in neurologic function postoperatively. GTR has been shown to provide patients with the best chance of PFS and OS. This is more easily accomplished for ependymomas and hemangioblastomas if there is a clear intraoperative tumor plane. Low-grade astrocytomas and ganglioneuromas are more infiltrative in nature and can be difficult to resect completely. Intraoperative electrophysiologic monitoring can provide a guide for resection because if the amplitude of the MEPs falls below 50% of baseline, this can indicate permanent damage to the motor pathways. Despite GTR, disease will recur in some patients, and adjuvant therapies are limited. Chemotherapy has not proved useful in most cases, and targeted therapy and improved drug delivery will be important avenues of exploration to improve upon surgical outcomes.

Pearls

- GTR is associated with improved outcomes overall, although this is less likely to be achieved for astrocytomas than for ependymomas.
- Adjuvant therapy plays a minimal role in the treatment of most IMSCTs. High-grade lesions have been treated with radiation therapy, but results continue to be disappointing in terms of PFS and overall survival. Chemotherapy may have some utility in the attempt to delay radiation therapy for young patients. However, studies have not shown significant improvements in survival or PFS compared with the natural history of the disease process for most patients.
- Intraoperative monitoring plays a critical role in the resection of IMSCTs. A decrement of greater than 50% in D-waves in addition to muscle MEPs signals a prolonged motor deficit, and the goal is to halt the resection before this loss of signal.
- Spinal fusion at the time of resection should be considered in patients who are at high risk for postoperative deformity. However, we tend to avoid simultaneous procedures because the hardware may interfere with MR imaging. We prefer to follow patients with serial X-rays.
- Recurrences of low-grade astrocytomas and ependymomas in patients who are ambulatory and have good neurologic function should be treated with reoperation and tumor debulking.

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47 Spine Tumors

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The classification of spinal tumors is based on their anatomical origin and extension, specifically with relation to the spinal cord (intra- or extramedullary) and dura (extra- or intradural). This chapter focuses exclusively on pediatric extradural tumors involving the spinal column. These tumors may arise from osseous or paravertebral structures and may be primary or metastatic. Spinal column tumors are rare in children and young adults, accounting for fewer than 1% of all spine and spinal cord tumors combined. The clinical symptoms, usually pain, allow early diagnostic consideration and evaluation. This chapter focuses on the more commonly encountered benign and malignant conditions, with an emphasis on diagnostic and treatment paradigms.

47.1 Epidemiology

Considered as a group, intramedullary, intradural extramedullary, and extradural spinal tumors account for 5 to 10% of all pediatric tumors of the central nervous system. Extradural primary or metastatic tumors account for approximately 50% of cases, followed by intradural intramedullary tumors (40%) and intradural extramedullary tumors (10%).¹⁻³ By comparison, pediatric brain tumors are six to seven times more common than pediatric spinal tumors. Extradural tumors are equally distributed throughout the mobile spine; sacral involvement is less common, except in the case of giant cell tumors and chordomas.

The primary tumors emphasized in this chapter include osseous tumors (osteoid osteoma, osteoblastoma, osteochondroma and osteogenic sarcoma, aneurysmal bone cyst [ABC], and eosinophilic granuloma). Malignant tumors (neuroblastoma, Ewing sarcoma, rhabdomyosarcoma, and chordoma) and metastatic tumors are also included here.

47.2 Clinical Symptoms

Spinal tumors in children may present with symptoms due to osseous or neural involvement, which causes pain, neurologic deficit, and/or spinal deformity. Most commonly, pediatric patients present with axial or radicular pain. The onset of symptoms may be acute in the case of vertebral collapse or epidural spinal cord compression. Slow-growing tumors may result in an insidious progression of symptoms. Persistent back pain, particularly when nocturnal, in a child should prompt diagnostic evaluation.⁴⁻⁶

The symptoms of spinal tumors in children are age- and location-dependent. Tumors causing compression of the spinal cord may produce upper motor neuron signs: weakness, hyperreflexia, hyperreflexia, clonus, Babinski sign, and sensory deficits. Lower motor neuron findings, including weakness, hypotonia, hyporeflexia, and sphincter dysfunction, may predominate in children with tumors involving the lumbar and sacral segments. The presentation of spinal tumors in infants and toddlers may be subtle, with irritability and regression of motor milestones.⁵

Spinal deformity, including kyphosis, scoliosis, and lordosis, occurs in up to 25% of children with spinal tumors and rarely is the sole presenting sign of a spinal tumor.^{5,7,8} The severity of spinal deformity generally relates to the extent of osseous destruction and neurologic deficit, although occasionally, a small tumor may cause a significant deformity.^{4,5,9} Spinal deformity may also develop after the treatment of spinal tumors; multilevel laminectomy and radiation therapy significantly increase the risk for deformity.^{10,11}

47.3 Diagnostic Imaging

Modern imaging permits a detailed anatomical visualization of the spinal and paravertebral structures, often allowing an accurate and concise differential diagnosis. Plain radiographs, often the initial study, can identify lytic or blastic lesions with a high rate of sensitivity.⁸ Additionally, spinal alignment can be assessed and the degree of scoliosis, if present, quantified.^{8,9} Computed tomography (CT) provides further detail and may reveal abnormalities not demonstrated on plain radiographs. Three-dimensional reconstruction of CT scans may also be useful for surgical planning. Magnetic resonance (MR) imaging adds anatomical detail of soft tissue and neural structures, demonstrating edema or compression of the spinal cord or nerve roots. Technetium bone scan may be helpful in selected cases, particularly when symptoms persist and the results of alternative imaging modalities are negative or equivocal.^{12,13} Spinal angiography is rarely indicated, although endovascular interventional techniques may be an important adjunct in the treatment of highly vascular lesions, such as ABCs and giant cell tumors.¹⁴⁻¹⁷

47.4 Treatment

The goals of treatment of spinal tumors are histologic diagnosis, complete tumor removal, and improvement or preservation of neurologic function, in addition to the correction and preservation of vertebral alignment. The treatment of choice for patients with symptomatic spinal cord compression is surgical decompression,⁶ although specific tumors, such as neuroblastomas, may be appropriately treated with primary radiation or chemotherapy.¹⁸⁻²¹ Corticosteroids may be given in anticipation of definitive treatment, although no specific agent or regimen has demonstrated superiority.⁵

47.4.1 Biopsy

Biopsy may be an appropriate initial procedure; CT-guided or fluoroscopically guided and open procedures have been described. CT-guided biopsy may be technically difficult with small, firm tumors and those in contact with neural or vascular structures. Additional concerns include seeding of tumor cells along the biopsy tract, although the risk for this often-cited complication may in fact be overestimated.²² Techniques including transpedicular approaches with closure of the biopsy tract with methylmethacrylate or hydroxyapatite may reduce

the risk for tumor seeding.²³ Given the small amount of material obtained by needle or trocar, there is a possibility of nondiagnostic tissue or sampling error. Although needle biopsy of spinal lesions has become widely used, the potential for nondiagnostic tissue or misdiagnosis is relatively high (18%) in the case of benign primary bone tumors.²⁴

Open biopsy may be performed by a transpedicular approach, laminectomy, or costotransversectomy. Laminectomy may be appropriate for lesions in the epidural space. However, for lesions of the vertebral body without epidural extension, laminectomy may result in the spillage of tumor cells into the epidural space.²⁵ The incision used for biopsy should be planned such that it can be included within resection margins should en bloc or wide excision be required.

Biopsy may be unnecessary in cases of suspected metastasis from a known primary tumor, or those in which the imaging characteristics are highly suggestive of a specific tumor type for which an initial attempt at complete resection is appropriate, such as ABC or osteoid osteoma.^{4,7,15}

Oncologic Staging

Boriani et al²³ emphasized the importance of oncologic staging in spinal bone tumors to evaluate accurately the relationships of histology, management, and outcome. They applied and expanded the principles of the Enneking system (► Fig. 47.1) for classifying the stages of musculoskeletal tumors to the spine.^{23,25} The Enneking staging system divides benign tumors into three stages (S1, S2, and S3) and local malignant tumors into four stages (IA, IB, IIA, and IIB). Two additional stages include metastatic high-grade intra- and extracompartmental tumors (IIIA and IIIB).^{23,25} This grading system incorporates clinical characteristics, radiographic features on CT, MR imaging and isotope scanning, and histologic diagnosis.

The first stage of benign tumors is S1 (latent, inactive), during which tumors do not grow, or do so very slowly. These tumors have well-defined margins and are contained within a true capsule and do not extend beyond the anatomical compartment of

origin. Surgery is indicated in cases of neural compression or instability.^{26–28} S2 tumors are benign or active and grow slowly; they are bordered by a thin capsule and a layer of reactive tissue. The results of technetium Tc 99 per technetate bone scans are often positive, depending on the presence of osteoblastic activity, which is associated with deposition of tracer. These lesions may be treated with en bloc resection or intralesional excision, both of which have reported low recurrence rates.^{15,29–32} The recurrence rate is further lowered by the addition of cryotherapy, embolization, or radiation therapy in appropriate cases.²³ S3 tumors are aggressive, rapidly growing benign tumors with or without a thin or incomplete capsule and have the potential to invade adjacent structures, creating a wide, reactive, and highly vascular pseudocapsule. Appropriate treatment for S3 lesions is en bloc resection or intralesional excision followed by adjuvant therapy. Despite aggressive measures, recurrence is common.^{8,23,33,34}

Low-grade malignant tumors, stages IA and IB, have no true capsule, are surrounded by a wide reactive pseudocapsule, and should be treated by en bloc resection and adjuvant radiotherapy. Stages IA and IB are differentiated by containment of the tumor within the vertebral body (type IA) versus invasion of the paravertebral compartments (type IB). High-grade malignant tumors, stages IIA and IIB, grow rapidly; there is no pseudocapsule, leading to the formation of local tumor nodules, and the continuous seeding of neoplastic cells results in distant seeding. These tumors often result in pathologic fractures. The favored surgical approach includes wide en bloc resection, if possible, followed by radiation and chemotherapy according to tumor type.^{2,33,35–40} Stages IIIA and IIIB are differentiated from stage II tumors by the presence of distant metastases.

Surgical Staging

The first proposed staging system for spinal bone tumors was described by Weinstein and McLain⁸ and was subsequently revised by a team at the Rizzoli Institute in Bologna.^{23,25} The resulting classification, the Weinstein, Boriani, Biagini surgical

Enneking System – Site	
T0	Benign tumor confined within a true capsule and anatomic compartment
T1	Aggressive benign or malignant tumor confined within anatomic compartment
T2	Lesion has spread beyond anatomic compartment

Enneking System – Histological grade		Enneking System – Metastasis	
G0	Benign lesion	M0	No metastasis
G1	Low-grade malignant lesion	M1	Local or remote metastasis
G2	High-grade malignant lesion		

Enneking System – Stage			
Stage	Grade	Site	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

Fig. 47.1 Enneking system for the classification of osseous tumors.²⁵

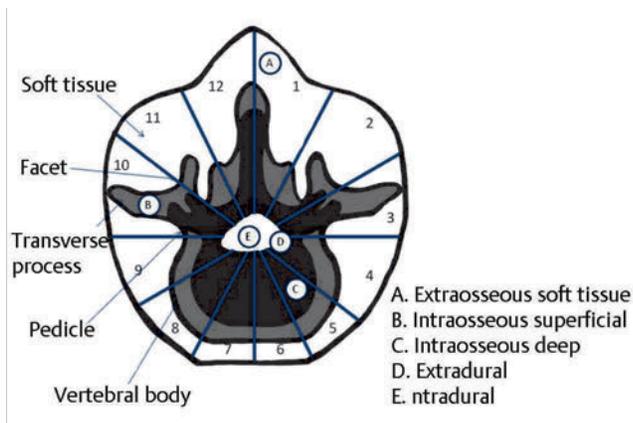


Fig. 47.2 The Weinstein, Boriani, Biagini surgical staging system. (After Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. Spine [Phila Pa 1976] 1997;22 (9):1036–1044.²³)

staging system (► Fig. 47.2), uses location of the tumor within the vertebral column and bases the surgical approach on specific anatomical factors. Each vertebra is divided into 12 transverse radiating zones and 5 concentric layers, beginning in the paravertebral extrasosseous region and extending to the dura. Tumor location is further categorized within longitudinal zones based on the number of levels involved. The oncologic and surgical staging of each tumor affords a plan for resection and adjuvant therapy based on the specific characteristics of each case.

47.4.2 Indications for Surgical Treatment

Indications for surgical treatment include the preservation of neurologic function and the restoration or maintenance of mechanical stability.^{6–8} For many benign pathological processes (e.g., ABC or osteoid osteoma), resection may be curative.^{4,15,27,41,42} Malignancies involving the pediatric spine (e.g., neuroblastoma and rhabdomyosarcoma)^{10,19,43} usually require surgical intervention, most often as a key element of a multidisciplinary approach. Surgical management may include biopsy, tumor resection, and spinal stabilization.

47.4.3 Surgical Treatment

For cases in which it is deemed appropriate, en bloc resection remains the operative goal. Three basic approaches for en bloc excision, based on anatomical considerations, have been described: vertebrectomy, sagittal resection, and posterior arch resection.^{7,8,23,25}

Vertebrectomy is indicated if the tumor is confined to the vertebral body and at least one pedicle is spared (zones 4–8 or 5–9). Vertebrectomy begins with a posterior approach and excision of the posterior elements at the involved level, with stabilization, followed by an anterior approach for vertebrectomy and

anterior reconstruction. Depending on the involved spinal level, anterior resection may be performed by an anterior cervical approach, a transpleural thoracotomy, or a thoracoabdominal or retroperitoneal abdominal approach.²³

Sagittal resection is indicated when the tumor involves the vertebral body eccentrically, including the pedicle or transverse process (zones 3–8 or 8–10). Sagittal resection includes a posterior approach for excision of the posterior elements and pedicle, followed by an anterior approach for partial vertebrectomy and the completion of pedicle and transverse process removal.²³

Resection of the posterior arch alone is indicated when the tumor is located exclusively in the posterior elements (zones 10–3). Surgery includes a wide laminectomy and exposure of the dura above and below the involved levels, with extension laterally to the pedicles.²³

Instrumentation and stabilization, when required in children, should take into consideration the location and extent of initial tumor involvement, the spinal levels, and anterior/posterior element deficiency. Future growth capacity and the potential for asymmetric growth and progressive deformity are additional considerations in the pediatric population. Removal of more than two laminae and facetectomy both significantly increase the incidence of postoperative deformity.¹¹ As a general principle, the fewest number of levels possible should be included in the construct. Asymmetric fusion should be avoided, and the use of nonbiological interpositional materials (methylmethacrylate) and growth factors, such as recombinant bone morphogenetic protein (rBMP), should be cautiously considered.^{7,23}

47.4.4 Managing Spinal Deformity and Instability after Treatment

The risk for instability and progressive deformity after treatment of spinal column tumors is significant. Reported rates of instability after pediatric spinal tumor resection range from 24 to 100%.^{5,8,9,11,45,46} This may result from bone destruction by the tumor, resection of the tumor or extensive bone removal, neurologic impairment caused by the tumor or its treatment, or postoperative irradiation.⁴⁷ Although the extent of bone removal correlates with deformity, the extent or safety of tumor resection should not be compromised.

The surgical approach itself may result in immediate instability, particularly if multiple spinal levels are involved or if facetectomy is required. Patients with tumors involving more than one spinal column are at significant risk for immediate instability. In cases of immediate spinal instability, instrumentation at the time of initial surgery is indicated. Cases not requiring immediate postoperative stabilization may nonetheless develop instability and progressive deformity. The risk for delayed instability is higher in younger patients and in those undergoing multilevel laminectomy in the cervical or thoracic region.⁴⁷ Radiation therapy significantly elevates the risk for delayed deformity, with a reported incidence from 10 to 100%.⁴⁷ The degree of deformity has been shown to relate to the initial radiation dose and the duration of follow-up.⁴⁵

Numerous techniques have been suggested to mitigate the risk for postoperative deformity: limiting the number of

laminectomies performed, avoiding facetectomy, immediate rather than delayed spinal instrumentation, preservation of the intraspinal ligament, laminoplasty, posterior lateral fusion, and prophylactic orthotic treatment.^{11,47–49} Laminoplasty has been advocated as a technique for minimizing postlaminectomy kyphotic deformity; however, some authors suggest that the rate of deformity is not decreased.⁴⁶ Replacement of lamina (not infiltrated by tumor) after resection restores normal anatomy and may facilitate reoperation and/or subsequent fusion if required.

Surgical indications for treatment of postsurgical or postirradiation spinal deformity include the degree and rate of progression, pain, and neurologic impairment. Otsuka et al⁴⁷ advocate posterior instrumentation and fusion for cases of moderately severe but flexible kyphosis. Cases of severe and/or rigid kyphosis are treated with a combined anterior release or decompression and fusion augmented by posterior instrumentation and fusion. They reported no pseudoarthrosis and an average kyphosis regression of 5% during follow-up. They reported that bracing was ineffective in preventing the progression of kyphosis in all cases.⁴⁷

47.5 Primary Bone Tumors

47.5.1 Osteoid Osteoma and Osteoblastoma

Osteoid osteoma and osteoblastoma are benign tumors and account for approximately 3% of all primary bone tumors.^{50,51} Osteoid osteoma accounts for 1.4% of primary spinal tumors and most commonly occurs in the second decade of life, with a male preponderance.²⁸ Ten percent of osteoid osteomas occur in the spine, with a large majority found in the posterior vertebral elements. Osteoblastoma is less common and has a peak incidence in the third decade of life.^{50,51} These tumors have a similar

histology, with bone formation by osteoblasts producing osteoid and woven bone. They are differentiated primarily by size, intraoperative appearance, and behavior. Osteoblastomas are larger than 1 to 1.5 cm and more vascular, and they are more likely to involve the vertebral body.⁵² Although exceedingly rare, cases of malignant transformation have been reported.⁵³ Osteoid osteomas typically have a sclerotic pattern, appearing hyperdense and expansile, without bone destruction. On MR imaging, high signal intensity on T2-weighted images of the surrounding muscle and bone is seen. Radiographically, osteoblastomas more commonly have a ground glass appearance on CT. They usually occur in cancellous bone of the lamina or pedicles of the cervical or lumbar spine.

Osteoid osteoma (► Fig. 47.3) commonly presents with localized pain, although radicular pain may be present because of nerve root irritation.⁵⁰ Other clinical findings may include point tenderness, scoliosis,⁹ and neurologic deficit.⁵¹ The pain is often severe and intermittent and is worsened by activity. Often, nocturnal pain relieved by nonsteroidal anti-inflammatory medications or aspirin is noted.⁵⁰ Osteoblastoma (► Fig. 47.4), shares many of the clinical features of osteoid osteoma; however, neurologic deficit is more common because of the larger size of this lesion.²⁸ The onset of symptoms may precede detectable abnormality on plain radiographs or CT. MR imaging and radioisotope bone scans may detect lesions not initially identified on plain radiographs or CT.^{54,55}

Observation alone may be appropriate management for small, intermittently or minimally symptomatic lesions consistent with osteoid osteoma. Spontaneous remission and involution may occur. In patients with persistent pain or neurologic deficit, gross total excision is the surgical goal. Osteoid osteoma appears firm and sclerotic with an occasional fibrotic or granulomatous component, whereas osteoblastoma more typically a friable, hemorrhagic mass, well circumscribed from the normal surrounding bone.



Fig. 47.3 This 5-year-old boy presented with severe dysesthetic pain of the right upper extremity. On examination, he had torticollis and weakness of the right deltoid and bicep. (a) Axial computed tomography shows a sclerotic lesion of the lateral mass and pedicle with a typical “ground glass” appearance, consistent with osteoid osteoma. (b) On sagittal T1-weighted magnetic resonance imaging, the lesion is hypointense. (c) The lesion was resected, and segmental posterior fusion with lateral mass screws was completed.

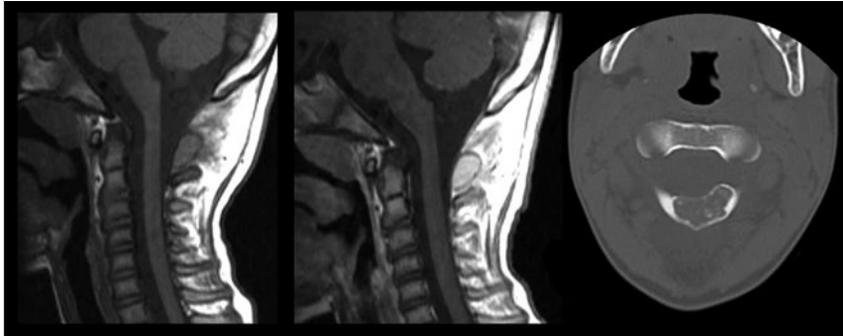


Fig. 47.4 This 17-year-old boy presented with persistent neck pain and torticollis. Osteoblastoma. (Courtesy of Dr. David Harter and Dr. Sarah Milla.)

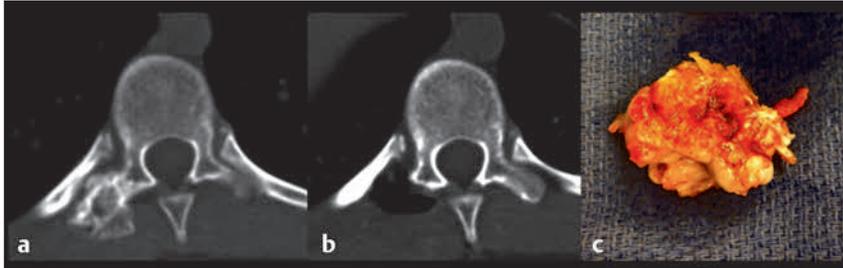


Fig. 47.5 This 15-year-old boy presented with back pain. (a) Axial noncontrast computed tomography demonstrates a lesion originating from the T10 transverse process. (b) The lesion was removed en bloc. (c) Osteochondroma.

Results of surgery are usually excellent for symptomatic relief and tumor control. However, the risk for local recurrence remains, with most series reporting a recurrence rate of approximately 10%.^{27,28,51} Intraoperative localization may be challenging, given the small size and sclerotic appearance of these lesions. Techniques, including preoperative CT-guided dye injection or guidewire placement and intraoperative radioisotope bone scanning, have been described.^{56,57} Although the estimated risk for radiation-induced malignancy is low (<1%),⁵⁸ reoperation rather than radiotherapy is recommended for recurrent or residual osteoid osteomas.^{27,50,51,53,55} CT-guided radiofrequency ablation and other techniques have also been described for the “deactivation” of osteoid osteoma with good results.^{59,60}

47.5.2 Osteochondroma and Osteosarcoma

Osteochondromas (► Fig. 47.5) account for 30 to 40% of benign osseous tumors and 4% of solitary spine tumors. They may occur as solitary, sporadic lesions or multifocally in the setting of an autosomal-dominant syndrome—hereditary osteochondromatosis. Approximately 1 to 7% of all osteochondromas occur in the spine. Solitary spinal lesions on average occur toward the end of the third decade of life, whereas multiple lesions occur earlier, toward the beginning of the third decade of life.²⁶ There is a significant male preponderance (2.5:1).^{26,61} Osteochondromas commonly affect the cervical spine, with approximately 50% of cases reported there.^{26,61,62} Osteochondromas can involve multiple contiguous vertebral levels and encroach upon the spinal canal and neural foramina, resulting in spinal deformity and neurologic impairment.^{26,61}

Given the cartilaginous quality of these tumors, plain radiographs are often normal. CT and MR imaging are often required

for the diagnosis. As for other benign spinal tumors, complete excision is usually curative, with excellent reported neurologic and functional outcomes.

Malignant transformation occurs in approximately 10% of cases, resulting in osteosarcoma. Although they are very uncommon in children, a small number of spinal osteosarcomas have been reported.^{63,64} The prognosis for spinal osteosarcoma remains poor, even with contemporary, multimodal treatment at experienced centers.^{65,66} The presence of metastatic disease and the inability to achieve en bloc resection are significant negative prognostic factors.^{65,66}

47.5.3 Aneurysmal Bone Cyst

ABCs occur most commonly in children and adolescents (median age, 10.2 years).⁶⁷ These expansile, vascular lesions have no known cause, although they have been reported to occur in conjunction with other pathologic conditions, such as giant cell tumor, fibrous dysplasia, and osteoblastoma.^{41,42,68} Histologically, the lesions often have a hemorrhagic component, with hemosiderin-containing macrophages; other features are multinucleated giant cells, fibrous tissue, and expansion of the cortical margins. Localized pain, worse with activity, is common. Neurologic symptoms occur as the lesion encroaches upon the neural foramina or spinal canal. Pathologic fracture or spinal instability may occur as the normal vertebral elements are replaced.

Radiographically, these lesions appear distinct—expansile, eccentrically located masses with fluid–fluid levels in the central region of trabeculae surrounded by a thin “eggshell” rim of cortical bone. They are often primarily located in the posterior elements, although they may also extend into the pedicle and vertebral body (► Fig. 47.6). There may be a significant soft tissue component, with variable enhancement on MR imaging or CT. Radionuclide bone scan may show areas of

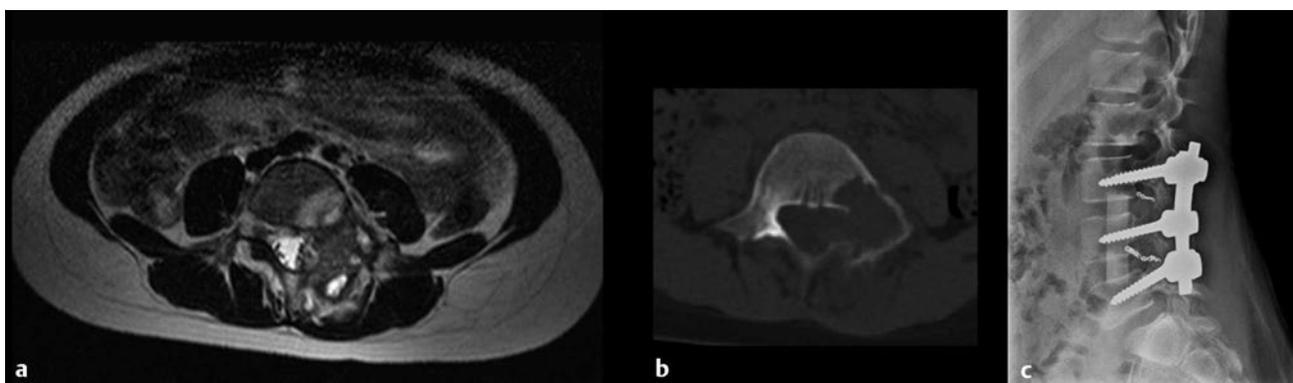


Fig. 47.6 This 8-year-old girl presented with persistent back pain that extended down the left lower extremity. She had paraspinal tenderness and weakness of the left dorsiflexors. (a) T2-weighted magnetic resonance imaging demonstrates a complex mass involving the lamina, pedicle, and vertebral body of L4, consistent with aneurysmal bone cyst. (b) Computed tomographic scan shows a thin rim of cortical bone. Preoperative angiography and embolization were performed. (c) The lesion was removed by a posterior approach, and primary reconstruction was performed with allograft and posterolateral fusion (note coils from embolization). (Courtesy of Dr. Joseph Dryer, New York University.)

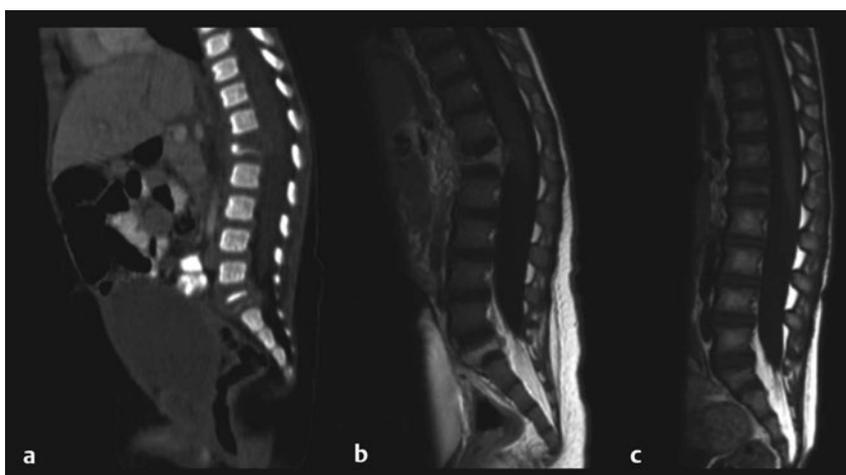


Fig. 47.7 At the age of 9 months, this infant boy presented with weight loss and a palpable skull mass. Biopsy confirmed Langerhans cell histiocytosis. (a) Computed tomographic scan with sagittal reconstruction. Lytic lesions of L1 and S1 are seen. Note the kyphotic deformity. (b) Magnetic resonance (MR) image with gadolinium. Vertebra plana with an associated enhancing epidural component. (c) Follow-up sagittal MR image after chemotherapy and bracing. There has been partial reconstitution of the vertebral bodies, and the degree of kyphosis has diminished.

peripheral uptake and a central area of hypoactivity within the cystic component. Arteriography often shows a highly vascular lesion with extensive collateral formation. Preoperative embolization, on a case-by-case basis, is advocated by many centers because blood loss may be significant.^{15,30,31} Embolization should be considered for large ABCs, those that involve multiple vertebral levels, and those with significant ventral extension. Intraoperative fatality from uncontrolled hemorrhage has been described.³¹ Although biopsy has been performed safely,^{24,69} the unique radiographic appearance of these lesions often obviates the need for histologic diagnosis before definitive surgical treatment.

ABCs are often locally aggressive, and gross total excision remains the goal. En bloc resection is usually not feasible; intralesional curettage is more commonly performed.^{14,15,30,31,41} Complete resection should be pursued because residual ABCs have a high propensity for progressive enlargement, with a recurrence of symptoms. Residual or recurrent ABC found after an initial attempt at resection is not uncommon, with reported rates of 10 to 14%.^{15,30,31} Although delayed recurrence is possi-

ble, recurrence within 6 months is more common.³¹ Resection of recurrent or residual ABC is the treatment of choice. These lesions may involve multiple vertebral segments or anterior and posterior columns, necessitating stabilization at the time of excision.^{14,15,30,31,41} Long-term follow-up is advisable because ABC may occur in conjunction with another condition, such as giant cell tumor or osteoblastoma, that may require additional treatment.^{41,42,68}

47.5.4 Eosinophilic Granuloma

Eosinophilic granulomas (► Fig. 47.7) are benign, destructive lesions characterized by the presence of abnormal histiocytes, known as Langerhans cells. They may be solitary or involve multiple organ systems, as in the following syndromes: histiocytosis X, Hand-Schüller-Christian disease, and Letterer-Siwe disease.⁵¹ Solitary eosinophilic granulomas occur most commonly in the skull, femur, mandible, ribs, pelvis, and spine. The cervical and thoracic segments are most commonly involved. Eosinophilic granuloma of the spine usually affects



Fig. 47.8 This 16-year-old boy presented with back pain and leg pain. (a) Sagittal magnetic resonance image with gadolinium identifies a large sacral mass. Angiography (b) before and (c) after embolization. Giant cell tumor. Resection was performed by a posterior approach.

the anterior column, with infiltration and erosion of the vertebral body and preservation of the adjacent intervertebral disks. The presentation is usually in childhood or adolescence with localized pain, which may be gradual or acute in onset; a history of minor trauma is not unusual. Neurologic deficit can also occur as a result of nerve root irritation or compression or spinal cord compression. Spinal deformity may also occur.

The radiographic findings of eosinophilic granuloma include a lytic, nonsclerotic, sharply defined lesion. Involvement of the adjacent vertebral segments and ribs may be identified. Vertebral body collapse may result in the characteristic vertebra plana. Plain radiographs and CT scans often show bony destruction and deformity. MR imaging may show enhancement of the soft tissue around the involved bone and also document involvement of the spinal canal or neural foramen. Because these lesions may be metabolically inactive, radioisotope bone scans may demonstrate no uptake within the lesion. Open or CT-guided biopsy is used to obtain tissue for definitive diagnosis.

The treatment of spinal eosinophilic granuloma is individualized based on the clinical presentation. For patients with acute neurologic deficit or significant spinal deformity, primary surgery may be indicated for diagnosis and the preservation or restoration of neurologic function and spinal stability.^{70,71} For patients without significant neurologic compromise or spinal deformity, observation or bracing alone may be warranted.⁷⁰ Radiotherapy has been shown to be effective, as has CT-guided intralesional corticosteroid injection.⁷²

47.5.5 Giant Cell Tumor

Most spinal giant cell tumors occur in the sacrum (► Fig. 47.8). They are more common in women. Spinal giant cell tumors are usually expansile and radiolucent. They may enlarge and involve the sacroiliac joints. Giant cell tumor outside the sacrum often involves the vertebral body. Imaging findings may be similar to those of ABC on CT, angiography, and nuclear bone scan. Like ABC, giant cell tumor is often locally aggressive, with high reported recurrence rates. En bloc resection is usually not feasible, and most are treated with internal curettage.^{29,41} Selective embolization may facilitate surgery and has also been used as treatment alone.¹⁷ Recently, successful medical therapy with bisphosphonates has been reported.^{73,74} Given the benign histologic nature of giant cell

tumor, radiation therapy is reserved for surgically inaccessible lesions.⁷⁵

47.6 Malignant Tumors

47.6.1 Neuroblastoma

As the most common extracranial solid tumor in children, and the most common neoplasm in infants, neuroblastoma is likely the most common malignant spine tumor treated by pediatric neurosurgeons. Arising from the sympathetic nervous system, adrenal glands, and ganglia of the thoracic, cervical, and pelvic regions, neuroblastomas may grow to massive size before the development of spinal involvement. Typically, epidural extension of the tumor occurs through one or more neural foramina, resulting in a dumbbell configuration. Ganglioneuroma and rhabdomyosarcoma may have a similar radiographic appearance.⁵ Metastatic spinal lesions may also occur, although usually as a late manifestation of disseminated disease. The thoracic and lumbar levels are most commonly affected. Interestingly, the survival of patients with symptomatic spinal cord compression is higher than that of patients without this finding.⁷⁶ Overall 5-year survival rates are 71%.¹⁹

Neuroblastoma with spinal involvement often appears as a dumbbell-shaped mass with a large paravertebral component (► Fig. 47.9). Compression and displacement of the spinal cord by epidural tumor are more common than mass effect due to osseous metastasis. Plain radiographs may demonstrate erosion of the pedicle, scalloping of the vertebral body, or widening of the spinal canal. These tumors usually appear homogeneous on noncontrast imaging and heterogeneous on postcontrast studies.

The indications for surgical decompression of epidural neuroblastoma are balanced against the degree and duration of neurologic deficit, the risk for postoperative deformity, and the chemo- and radiosensitivity of this tumor.¹⁹ High-risk patients with spinal involvement and minimal or no neurologic deficit should be offered chemotherapy. Patients with significant deficit due to cord compression may respond to chemotherapy, with the understanding that some may require operation for progressive neurologic deficit. Chemotherapy may be avoided in low-risk patients who are potentially curable with operation alone.⁷⁶⁻⁷⁸ Patients treated with surgery or chemotherapy for epidural disease often have residual neurologic dysfunction or spinal deformity. Punt et al reviewed 122 patients with spinal

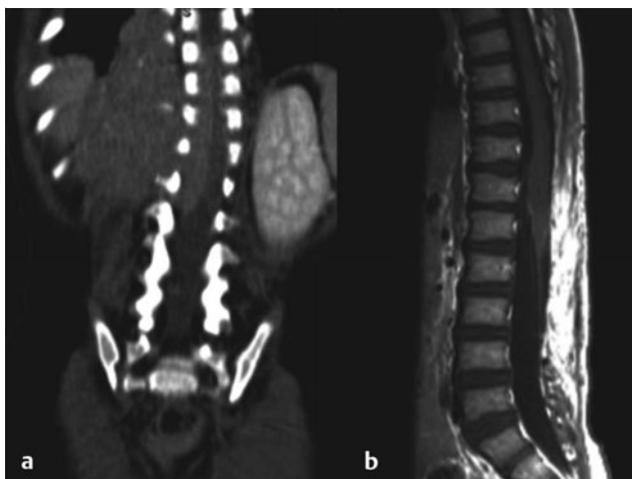


Fig. 47.9 This 11-month-old boy presented with irritability and progressive paraparesis. (a) Computed tomographic scan with coronal reconstruction demonstrates a large thoracic paravertebral mass extending through multiple neural foramina, with spinal cord compression. Multilevel laminectomy rather than laminoplasty was performed because of bone infiltration. Neuroblastoma. (b) Sagittal postcontrast magnetic resonance image shows moderate kyphotic deformity, no evidence of tumor.

cord compression due to neuroblastoma. After a median 8-year follow-up, most (71 of 99) had problems: motor impairment (43%), scoliosis (31%), impaired bladder function (26%), constipation (19%), impaired cutaneous sensibility (17%), growth delay (14%), and neuropathic pain (5%). The initial treatment had no clear impact on the frequency of late effects.⁷⁸ The Pediatric Oncology Group reviewed 83 patients treated with laminectomy or laminectomy with chemotherapy and/or radiotherapy versus chemotherapy or radiation alone. They reported scoliosis rates of 29% and 2% for patients with and without laminectomy, respectively. They advised laminectomy only for patients with progressive neurologic symptoms after the initiation of chemotherapy.¹⁹

47.6.2 Rhabdomyosarcoma

Rhabdomyosarcoma accounts for 8% of pediatric solid tumors. Spinal involvement may present in a manner similar to that of neuroblastoma, a dumbbell-shaped tumor with a large paraspinous component (► Fig. 47.10). Rhabdomyosarcoma, like neuroblastoma, is sensitive to chemotherapy and radiation therapy; the rationale for surgical intervention is similar.⁷⁹

47.6.3 Ewing Sarcoma

Ewing sarcoma is the most common nonlymphoproliferative primary malignant spinal tumor in children. There is a spinal origin in 3 to 10% of cases, and metastatic lesions of the spine may also occur. Ewing sarcoma typically presents between the ages of 10 and 20 years; the sacrococcygeal region is most commonly involved, followed by the lumbar and thoracic levels. Lesions are typically centered in the vertebral body but can extend into the posterior elements. Plain radiographs demonstrate areas of bone lysis, expansion, or sclerosis (► Fig. 47.11).

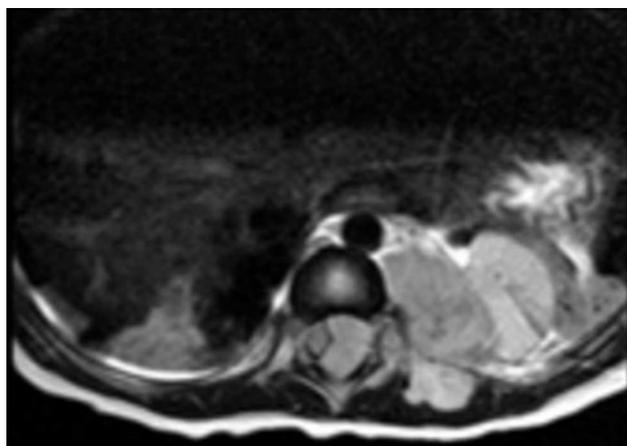


Fig. 47.10 This 2-year-old girl presented with progressive paraparesis and a large paravertebral component with displacement and compression of the spinal cord. Rhabdomyosarcoma. She underwent laminoplasty laminectomy and subsequent thoracotomy for tumor resection followed by chemotherapy.

CT and MR imaging demonstrate a surrounding soft tissue mass and reactive change; however, no specific radiographic criteria are established. Histologically, these lesions are highly mitotic, poorly differentiated and pleomorphic. Intraoperatively, they appear firm, gray, and friable, with hemorrhage and necrosis.

The treatment of Ewing sarcoma has evolved, and outcomes have improved considerably.^{35,36,80} Current treatment recommendations include biopsy with initial chemotherapy and radiation for high-grade malignancies, with second-look surgery for residual tumor when appropriate. Resection for histologically low-grade tumors, followed by adjuvant chemotherapy and radiation, is suggested.^{5,37,81}

Location remains an important prognostic factor. Sacral lesions often reach a large size before diagnosis, making en bloc resection difficult.³³ Lesions of the mobile spine often present earlier, facilitating diagnosis and treatment. Attempts at resection should avoid piecemeal or intralesional approaches and should favor en bloc resection with negative tumor margins.^{33,35} Other favorable factors include younger age (younger than 10 years), tumor volume of less than 100 mL, a positive response to chemotherapy (>90% volume reduction), and en bloc resection.³⁵ Negative prognostic factors include metastatic disease, tumor larger than 8 cm, elevated white blood cell count and erythrocyte sedimentation rate, and less than 90% reduction of tumor volume with chemotherapy.⁴⁰ Current estimates for 5-year survival after multimodality treatment range from 33 to 74%.^{33,36}

47.6.4 Chordoma

Chordoma is a locally aggressive tumor derived from the malignant transformation of notochordal remnants. Chordoma is a rare tumor during childhood, accounting for 5% of all malignant primary bone tumors. Chordomas in children are most commonly located in the midline of the skull base at the sphenocipital junction, followed by the mobile spine, and finally the sacrococcygeal region.⁸² They are slow-growing tumors, and symptom progression (pain, numbness, and weakness) is often

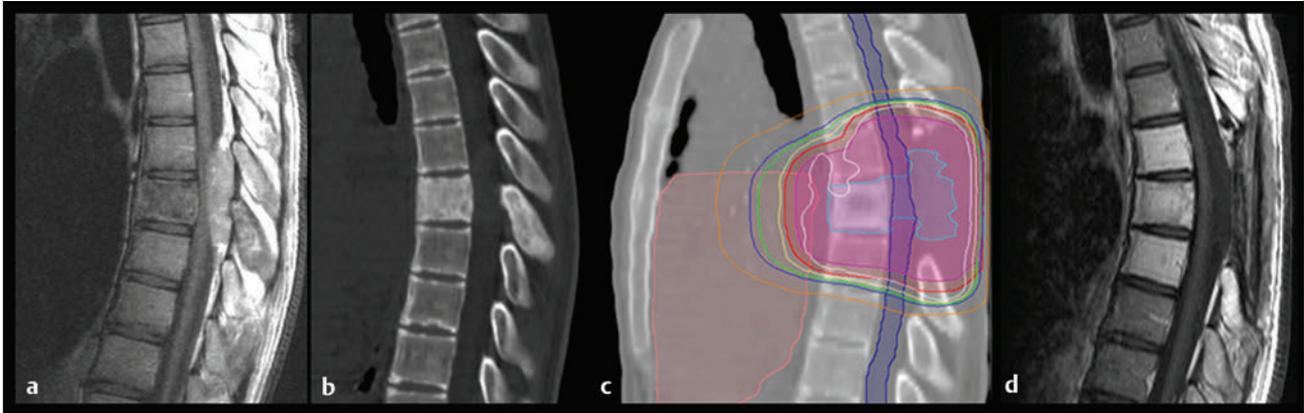


Fig. 47.11 This 16-year-old boy presented with a progressive paraparesis, back pain, and a midthoracic sensory level. He underwent emergent laminectomy for resection of an epidural tumor followed by adjuvant chemotherapy and radiotherapy. Ewing sarcoma. (a) Contrast-enhanced sagittal magnetic resonance (MR) image. (b) Sagittal reconstruction of a computed tomographic (CT) scan. (c) Immediate postoperative CT scan with radiation dosimetry. (d) Follow-up contrast-enhanced sagittal MR image 5 years after surgery. No active tumor is seen. Laminectomy defect and moderate thoracic kyphosis. (Courtesy of Dr. David Harter, Dr. Elizabeth Raetz, and Dr. Ashwatha Narayana.)

Tumortype	Age	Location	Histology	CTfindings	MRIfindings	Treatment
Osteoma	1 st -2 nd decade	Cervical and lumbar, posterior elements	Hypodense tumor surrounding normal trabeculae	Low density center with surrounding sclerosis, <1-1.5 cm	Nidus-T1 isointense, T2 hypointense, Nidus enhancement	Resection or ablation
Osteoblastoma	3 rd decade	Cervical and lumbar, posterior elements	Distinct margin, osteoblasts, osteoclastic giant cells	Low density center with surrounding sclerosis, >1 cm	Reactive marrow, soft tissue edema	Resection
Osteochondroma	2 nd decade	Thoracic and lumbar, posterior elements	Cartilage formation	Ring/arc calcifications	Cartilage cap, T1 hypointense – T2 hyperintense,	Resection
Osteosarcoma	3 rd -6 th decade	Lumbar and sacral, posterior elements	Spindle cells, immature bone	Variable, lytic or sclerotic	T1 hypointense, T2 hyperintense	Multimodal, excision, XRT and chemotherapy
Aneurysmal bone cyst	2 nd decade	Equal, posterior elements, pedicle and vertebral body	Cavernous cyst with walls of woven bone	Expansile, eggshell cortex	Fluid levels, hemorrhage, soft tissue edema	Resection +/- preoperative embolization
Eosinophilic granuloma	1 st -2 nd decade M>F	Cervical, thoracic, vertebral body	Langerhans' cells	Lytic destruction, vertebra plana	Preserved disc spaces, enhancing epidural mass	Observation, biopsy, excision

Fig. 47.12 Common characteristics of pediatric epidural spinal tumors.

insidious. Dissemination, although rare, has been reported within and outside the neuraxis.⁸³

Given that the notochord is the embryologic source of the nucleus pulposus, initial involvement of the vertebral body is expected. Radiographically, osteolysis with a large associated soft-tissue mass is typical. Histologically, chordomas are usually contained within a pseudocapsule and are characterized by the presence of physaliphorous cells containing intracytoplasmic vacuoles and abundant mucin.^{82–84}

Current surgical recommendations include en bloc resection with tumor-free margins. Proton beam radiotherapy is recommended for residual tumor or recurrence.⁸⁵ Reported 5-year survival rates approximate 50%.^{84,86}

47.6.5 Epidural Metastasis

Children with solid malignant tumors may develop an epidural spinal metastasis or osseous metastasis with extension into the epidural space, causing spinal cord compression. Studies report that from 3 to 5% of all children with malignant solid tumors develop epidural spinal metastases.^{87,88} Among children with spinal cord compression, 17.9% had Ewing sarcoma, 7.9% neuroblastoma, 6.5% osteosarcoma, and 4.9% rhabdomyosarcoma. Other diagnostic considerations include lymphoproliferative disorders, sarcomas, germ cell tumors, and others. Spinal cord compression (weakness, pain, or myelopathy) occurs as the presenting symptom in approximately 10% of pediatric patients with epidural metastases.⁸⁷ The treatment and prognosis depend upon the primary tumor; of particular importance is sensitivity to adjuvant therapy, including chemotherapy and radiation therapy.⁸⁸

47.7 Conclusion

Pediatric spinal tumors often present with pain. The diagnosis is often suggested by the clinical history. Physical examination may show signs of spinal deformity or neurologic deficit. Imaging with plain radiographs often shows scoliosis or osteolytic or osteoblastic lesions. MR imaging and CT allow excellent visualization of the neural and osseous structures. Biopsy may be useful to guide definitive therapy, although it is not uniformly required. Surgery for benign lesions should be undertaken with curative intent. For locally aggressive benign tumors and contained malignancies, an attempt at en bloc resection followed by adjuvant therapy is suitable. Spinal deformity may be a presenting symptom or may result from treatment and should be treated if progressive or symptomatic. Multidisciplinary approaches have improved the functional and oncologic outcomes for many of these disorders.

47.8 Acknowledgments

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Pearls

- Radionuclide bone scan should be considered for children with persistent symptoms and negative findings on radiography, CT, and MR imaging.
- Preoperative embolization should be considered for ABCs and giant cell tumors.
- The surgical goal for benign spinal tumors is cure.
- Locally aggressive tumors and primary malignancies are ideally treated with en bloc resection and adjuvant therapy.
- Spinal instability is common among children with spinal tumors and should be treated when it is progressive or symptomatic.
- Children have a significant chance of meaningful recovery, even when they present with severe neurologic impairment due to neoplastic spinal cord compression.

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48 Neurofibromatosis 1 and 2

Ian F. Pollack

Neurofibromatosis is a descriptive term that was coined by Frederick von Recklinghausen in 1882 to characterize the cutaneous tumors of two patients that were thought to be composed of a combination of neural and mixed cellular elements. This diagnostic category was later expanded to incorporate an array of dermatologic, ocular, and nervous system manifestations; thus, it was included with the broader group of disorders referred to as phakomatoses. In the ensuing decades, investigators realized that patients with NF could be categorized into distinct clinical groups based on the pattern of neural and extraneural manifestations.¹ Improvements in imaging techniques and advances in molecular genetics have facilitated these efforts and allowed clinicians to confidently classify patients as having neurofibromatosis 1 (NF-1, previously known as *peripheral neurofibromatosis*) or neurofibromatosis 2 (NF-2, previously known as *central neurofibromatosis*), and they have also identified phenotypically similar variants that are distinct entities.^{2,3}

The importance of recognizing these disorders stems from the fact that the natural history of a neoplasm, such as a peripheral nerve tumor or an optic glioma, may be significantly different depending on whether or not the lesion arises in a person with NF. In addition, the indications for therapeutic intervention, the hierarchy of treatment options, and the long-term management goals may differ substantially for patients with NF-related versus sporadic tumors. Finally, recognition of the diagnosis is an essential step in providing appropriate multidisciplinary evaluation and counseling to affected patients and their families. This chapter focuses on the diagnostic and therapeutic issues that arise in children with NF-1 and NF-2; other phakomatoses are discussed in the following chapter.

48.1 Epidemiology, General Diagnostic Criteria, and Molecular Pathogenesis

NF-1 is one of the most common genetic disorders, affecting 1 in 3,000 to 1 in 4,000 people.^{4,5} The mode of inheritance is autosomal-dominant, and approximately 50% of cases arise sporadically as new mutations. The syndrome results from mutations or deletions of a gene on chromosome 17q11.2 that encodes a large protein called neurofibromin. A portion of this protein is a guanosine triphosphatase (GTPase) activator^{6,7} that plays a role in signal transduction by favoring conversion of the active GTP-bound form of Ras and related G-proteins to the inactive guanosine diphosphate (GDP)-bound form.⁸ The NF-1 gene functions as a classic tumor suppressor gene in that loss of both alleles is needed for tumorigenesis. Because patients with NF-1 are born with only one normal copy of the gene, a single mutation or deletion that inactivates the second allele is theoretically sufficient to favor tumor formation,⁹ although additional molecular events may also contribute.¹⁰

Affected patients exhibit a combination of café au lait macules, Lisch nodules (iris hamartomas), axillary and inguinal

freckling, skeletal lesions such as sphenoid wing dysplasia and thinning of long bone cortices, and optic gliomas, as well as an increased incidence of other central nervous system and systemic tumors.^{10–15} Diagnostic criteria that reflect the diverse manifestations of NF-1 were proposed at a National Institutes of Health (NIH) Consensus Development Conference¹⁶ (see box “NIH Consensus Criteria for the Diagnosis of Neurofibromatosis 1”¹⁶). They were devised, in part, for high specificity (i.e., to have a low rate of false-positive diagnoses). Because many of the characteristic stigmata, such as Lisch nodules, are not usually apparent in infancy, ongoing follow-up is sometimes required to establish the diagnosis conclusively. In a large study of patients with sporadic NF-1, 54% of children met diagnostic criteria by 1 year of age, 97% by 8 years, and 100% by 20 years.¹⁷ The exclusion of non-NF-1 variants, such as Proteus syndrome (the original “elephant man” disease that was mistaken for NF-1) and Legius syndrome, has been facilitated by genetic testing when clinically warranted.²

NIH Consensus Criteria for the Diagnosis of Neurofibromatosis 1

The diagnostic criteria are met if a patient has two or more of the following:

- Six or more café au lait macules that have a maximum diameter of more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
- Two or more neurofibromas of any type, or one or more plexiform neurofibromas
- Freckling in the axillary or inguinal region
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A characteristic osseous lesion, such as sphenoid wing dysplasia or thinning of the long bone cortices, with or without pseudarthrosis
- A first-degree relative (i.e., parent, sibling, or child) with NF-1 by the above criteria

Source: National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference statement. Arch Neurol 1988;45(5):575–578.¹⁶

NF-2 is less common than NF-1, affecting 1 in 25,000 to 1 in 50,000 people.^{18,19} This disorder reflects mutations or deletions involving a gene at chromosome region 22q12 that encodes a protein referred to as merlin (*moesin-, ezrin-, and radixin-like protein*); merlin is involved in linking cytoskeletal elements with plasma membrane proteins.²⁰ Affected patients have a combination of eighth nerve and other cranial nerve neurilemmomas, meningiomas, glial neoplasms, neurofibromas, and juvenile posterior subcapsular cataracts (see box “Consensus Criteria for the Diagnosis of Neurofibromatosis 2”¹⁶). As in patients with NF-1, the diagnosis in patients without a positive family history may be difficult initially because many children will not manifest sufficient findings to satisfy diagnostic criteria

conclusively, and they may present at a young age with isolated nervous system tumors, such as spinal cord ependymomas and unilateral vestibular schwannomas.^{21,22} In such “suspected” cases, ongoing surveillance is warranted.

Consensus Criteria for the Diagnosis of Neurofibromatosis 2

The diagnostic criteria are met if a person has either of the following:

- Bilateral eighth nerve masses seen with appropriate imaging techniques, such as magnetic resonance imaging or computed tomography
- A first-degree relative with neurofibromatosis 2 and a unilateral eighth nerve mass or two of the following:
 - Neurofibroma
 - Meningioma
 - Glioma
 - Neurilemoma
 - Juvenile posterior subcapsular cataract

Source: National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference statement. Arch Neurol 1988;45(5):575–578.¹⁶

A distinct subgroup of patients with features of NF-1 and NF-2 exhibit signs restricted to certain segments of the body. In the most typical situation, patients will have café au lait macules and neurofibromas on one extremity or one-half of the body and may have Lisch nodules in the ipsilateral eye. This so-called segmental form of NF-1 accounts for 5% of patients with NF-1 and arises from mosaicism, in which mutations of the *NF1* gene occur at some time after fertilization in the developing embryo.^{3,13,23} If gonadal progenitors are spared (i.e., there is just somatic mosaicism), then this form of the disorder is not genetically transmissible. If both gonadal and somatic cells are involved, then a potential exists for genetic transmission, which varies from nearly zero (if a small percentage of gonadal cells are involved) to 50% (if all gonadal cells are involved). A segmental form of NF-2 has also been suggested for patients who have multiple discrete neurilemmas involving peripheral nerves of an extremity without central features of NF-2.²³

Even among patients with typical (nonsegmental) NF-1 or NF-2, there is significant variability in the severity of manifestations between members of different families. The basis for this symptomatic heterogeneity may in part reflect differences in the specific site of mutations in the *NF1* or *NF2* genes themselves²⁴: patients with large deletions involving the *NF1* locus and surrounding genes tend to have a more severe phenotype than those with point mutations,²⁵ whereas those with small in-frame gene deletions have a milder variant.²⁶ The results of increasingly available genetic tests, such as protein truncation assays, fluorescent in situ hybridization, and direct sequencing, correlated with the clinical features, should shed further light on this issue during the next few years and should also help to resolve the diagnostic uncertainty that often surrounds patients who meet only one criterion for NF-1 or NF-2. However, an important caveat in interpreting these genetic

studies is that the exact features of NF-1 and NF-2 can vary widely within a single family (in which all affected individuals should have an identical *NF* mutation), reflecting the likely involvement of other disease-modifying genes or interacting environmental factors. Thus, contemporary genetic testing can predict the occurrence of NF-1 or NF-2, but not its severity in most cases.²⁴

48.2 Diagnostic Evaluation

Box “Suggested Screening Studies for Children with Proven or Presumptive Neurofibromatosis 1” and box “Suggested Screening Studies for Children with Proven or Presumptive Neurofibromatosis 2” summarize the baseline evaluations that are recommended in children with proven or suspected NF-1 or NF-2. Similar suggestions for health supervision in children with NF-1 have been published by the Committee on Genetics of the American Academy of Pediatrics.²⁷ Such recommendations represent guidelines rather than requirements, and as such, they are followed with flexibility and judgment. They incorporate a detailed screening of the major systems involved by each of the disorders, particularly the skin, eyes, nervous system, and spine, and provide a basis for a more detailed evaluation of other systems if concerning findings are detected on a screening evaluation. For example, children with NF-1 or NF-2 do not undergo routine imaging of the chest and abdomen, but such studies are employed for those who present with symptoms of dyspnea, abdominal discomfort, or distention, which may be referable to an enlarging thoracoabdominal tumor. Similarly, a comprehensive endocrine evaluation coupled with cranial magnetic resonance (MR) imaging is pursued in children with NF-1 who manifest precocious puberty, growth delay, or other evidence of endocrinopathy that may be related to hypothalamic involvement by tumor. Finally, because children with NF-1 often exhibit varying degrees of cognitive impairment that may interfere with their school performance and socialization,^{28,29} detailed neuropsychological testing is often pursued, but the need for this testing is determined on a case-by-case basis.

Suggested Screening Studies for Children with Proven or Presumptive Neurofibromatosis 1

- Annual clinical examination including neurologic assessment and dermatologic evaluation
- Annual ophthalmologic examination
- Magnetic resonance (MR) imaging examination of the head
 - Children diagnosed before 5 years of age
 - Children with new neurologic deficits, visual loss, or endocrinopathy
- MR examination of the spine and plain radiographs
 - Children with scoliosis
 - Children with back pain, radiculopathy, or long tract signs referable to the spine
- Neuropsychological and developmental testing
 - Children with learning, speech, or socialization difficulties or impaired fine motor skills
- Genetic counseling should be offered to the family at diagnosis and as needed on an ongoing basis.

Suggested Screening Studies for Children with Proven or Presumptive Neurofibromatosis 2^a

- Neurologic examination
- Ophthalmologic examination
- Audiogram
- Magnetic resonance imaging of the head and spine
- Genetic counseling should be offered to the family at diagnosis and as needed on an ongoing basis.

^aThe frequency with which these tests are repeated depends on whether abnormalities are identified on the initial evaluation. At the least, all tests should be repeated approximately every 3 to 5 years. Annual examinations are recommended for children with known lesions.

An important element in the evaluation of such children is the need for a comprehensive approach to patient care, often best provided in the setting of a multidisciplinary clinic. This approach facilitates efforts to diagnose and treat the child as an individual rather than as a collection of affected organ systems and ensures that management and counseling proceed in a coordinated fashion. A discussion of the major nonneurologic and neurologic manifestations of these disorders and their diagnosis and management is provided below.

48.2.1 Nonneurologic Manifestations

Because both NF-1 and NF-2 are multisystem disorders, patients often present with symptoms and signs not directly referable to a nervous system tumor. Appropriate recognition of the significance of these findings and knowledge of the indications for diagnostic and therapeutic intervention are essential for optimizing functional outcome.

Neurofibromatosis 1

Café au lait macules and axillary freckling are often a source of concern but are of no serious clinical significance. These lesions result from abnormal collections of melanin pigment in affected melanocytes, which harbor loss or inactivation of both *NF1* alleles.³⁰ Café au lait macules, in particular, can occur in a variety of syndromes other than NF-1; thus, their detection in an infant or young child does not signal the need for extensive neurodiagnostic imaging in the absence of other clinical stigmata or a family history of NF-1, but it does warrant conscientious pediatric follow-up. Similarly, Lisch nodules simply represent melanocytic iris hamartomas; although these lesions increase in frequency during childhood and are present in more than 90% of affected patients by the completion of puberty,^{17,31} they do not interfere with vision.

In contrast, skeletal manifestations can be of major long-term functional significance. Congenital bowing and/or dysplasia of the long bones, particularly the tibia, may lead to pathologic fractures that resist healing.^{14,32} Osseous dysplasia can involve the sphenoid bone as a congenital or acquired process,³³ which leads to herniation of the temporal lobe contents into the orbit and, in some cases, produces pulsatile proptosis and seizures (► Fig. 48.1). Because few patients exhibit progressive

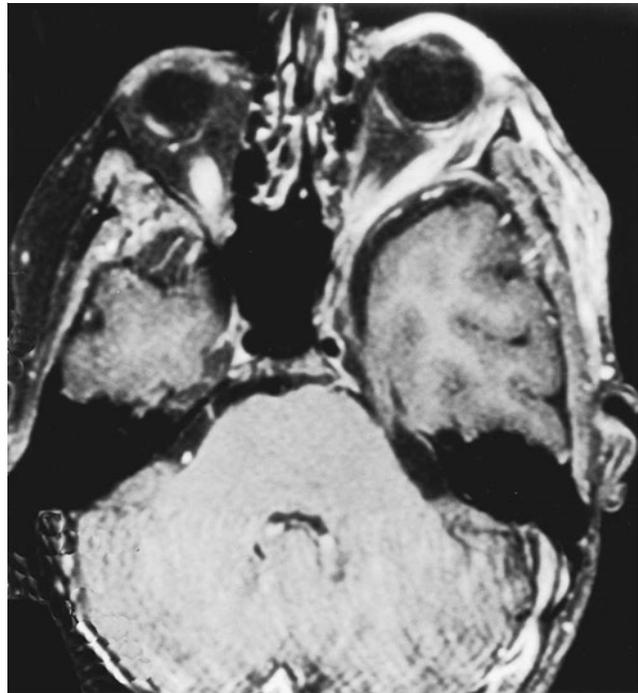


Fig. 48.1 This axial T1-weighted magnetic resonance image shows left sphenoid dysplasia with protrusion of the temporal dura into the posterolateral orbit and resultant proptosis.

impairment from this deformity, operative intervention should be limited to those children with worsening proptosis in the absence of another explanation, such as an orbital plexiform neurofibroma, or with intractable seizures from the involved temporal lobe. In such rare cases, reconstruction with split-thickness calvarial grafts or rib grafts may be beneficial.

Spinal manifestations are also common, even in the absence of neoplastic involvement. Some degree of scoliosis is present in most patients with NF-1,^{14,32} but it often does not require specific therapy. However, in a small percentage of children with NF-1, the scoliosis is severe and rapidly progressive. Because many of these patients will be found to have an intra- or extra-axial neurofibroma, which may need to be addressed in conjunction with a spine-straightening procedure, MR imaging is an essential step in the preoperative evaluation. Regardless of the cause for the scoliosis, the rapid progression that occurs in some children mandates that vigilant follow-up and expeditious intervention be pursued to avoid severe deformity. Patients often require a combination of bracing, anterior and posterior fusion, and instrumentation to treat this problem. In such cases, the use of MR imaging-compatible hardware is advisable because these patients generally require long-term surveillance for tumor growth. Other, less serious spinal manifestations include vertebral scalloping and nonneoplastic widening of the neural foramina from dural ectasia.³⁴ Most cases require no specific intervention. An additional phenomenon that is occasionally observed in patients with NF-1 is segmental hypertrophy.⁵ This may involve a portion of the head or one of the extremities. Although there is usually an underlying neoplastic component in the involved area, the deformity often exceeds that directly attributable to the tumor. It remains uncertain

whether this reflects generalized mesenchymal dysplasia in the involved area or a combination of neurogenic and humoral factors initiated by the tumor. Children with NF-1 have also been noted to have an increased incidence of central precocious puberty and growth hormone deficiency; in some cases, this is independent of any radiologically apparent hypothalamic tumor involvement.

In addition to the nervous system tumors discussed below, patients with NF-1 are also at risk for a variety of systemic malignancies, including leukemia, pheochromocytoma, rhabdomyosarcoma, adenocarcinoma of the ampulla of Vater, melanoma, and non-Hodgkin lymphoma, presumably reflecting either loss or inactivation of the second *NF1* allele or other secondary genetic events.^{5,35,36}

Neurofibromatosis 2

In patients with NF-2, the major serious nonneural manifestation is the development of posterior subcapsular cataracts, which are detected in 85% of affected individuals and often progress with age.¹² Because these lesions can threaten vision, conscientious ophthalmologic follow-up is required, and surgical removal of the cataract may be indicated. In patients with unilateral visual loss secondary to one of these lesions, particular attention must be directed to monitoring and protecting vision in the contralateral eye, which includes preserving facial nerve function to maintain eye closure and corneal protection.

48.2.2 Neurologic Manifestations

Children with either NF-1 or NF-2 may present with neoplasms of the brain, spinal cord, and peripheral nerves, but the most common types of lesions differ significantly in these two syndromes. In addition, patients with NF-1 may exhibit a variety of nonneoplastic neurologic manifestations that must be distinguished from tumors to avoid unnecessary intervention. The most common processes are summarized below, along with management approaches.

Neurofibromatosis 1

Focal Areas of Increased Signal on T2-Weighted Magnetic Resonance Imaging

By far the most common abnormalities on MR imaging in patients with NF-1 are foci of increased signal on T2-weighted images without mass effect or contrast enhancement, so-called unidentified bright objects (UBOs; ▶ Fig. 48.2). These foci, which are detected in 60 to 80% of children with NF-1,^{37,38} may be solitary, multiple, or confluent and are seen most commonly in the basal ganglia, internal capsule, brainstem, and cerebellum. In view of the high frequency of these lesions in patients with NF-1, it has been suggested that their presence be added to the diagnostic criteria for this syndrome. On serial images in individual patients, foci of T2 signal abnormality often increase in frequency and number early in childhood, then regress later in childhood.^{37,38} This pattern suggests that these lesions represent age-related abnormalities in myelination. Some groups have noted that the presence and extent of these signal abnormalities correlate with the detection of learning disabilities,

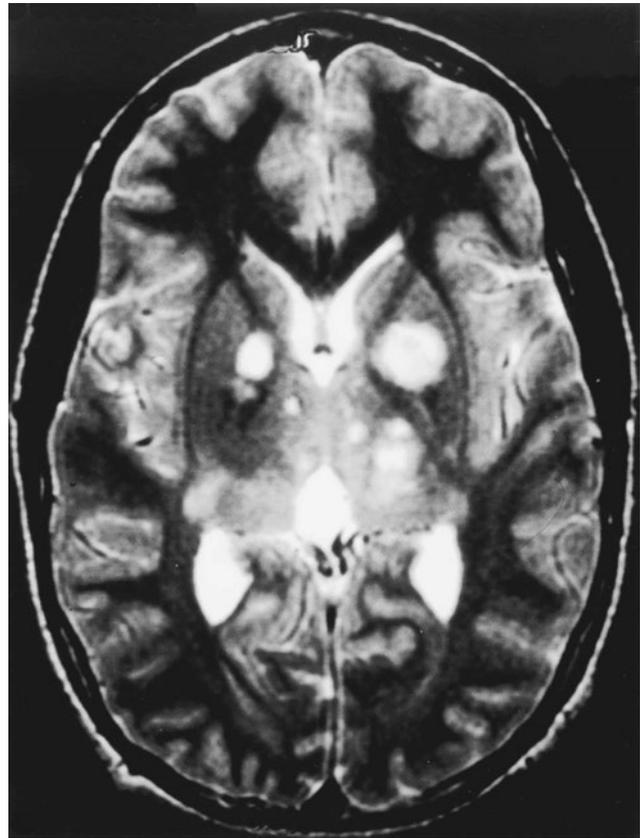


Fig. 48.2 This axial T2-weighted magnetic resonance image demonstrates the characteristic areas of T2 signal abnormality that are commonly detected within the basal ganglia and occasionally within the cerebellum and other regions of the brain in patients with neurofibromatosis type 1.

which are encountered in at least 25% of patients with NF-1, although others have failed to note a clear relationship.^{28,29} Similarly, it remains uncertain whether patients with UBOs are at increased risk for the development of central nervous system neoplasia compared with patients who have NF-1 without this finding, although at least one group has noted such a trend.³⁹

Because UBOs themselves typically follow a benign course, their detection in an otherwise asymptomatic child does not signal the need for serial MR imaging. However, this conservative follow-up approach should not be applied to childhood lesions that exhibit atypical MR imaging features, such as mass effect or enhancement, or that are associated with focal neurologic symptoms. Such a follow-up approach should also not be followed in older patients with new lesions. In all these instances, the natural history remains uncertain.

Optic Pathway Lesions

The second most common imaging abnormality in NF-1 is optic pathway glioma, detected in at least 15% of patients (▶ Fig. 48.3). Several characteristic lesion types may be seen. The mildest abnormalities consist only of thickening of one or both optic nerves⁴⁰; although most such lesions are low-grade gliomas, others may simply represent hyperplasia of the optic nerve sheath. Other patients exhibit a globular thickening of

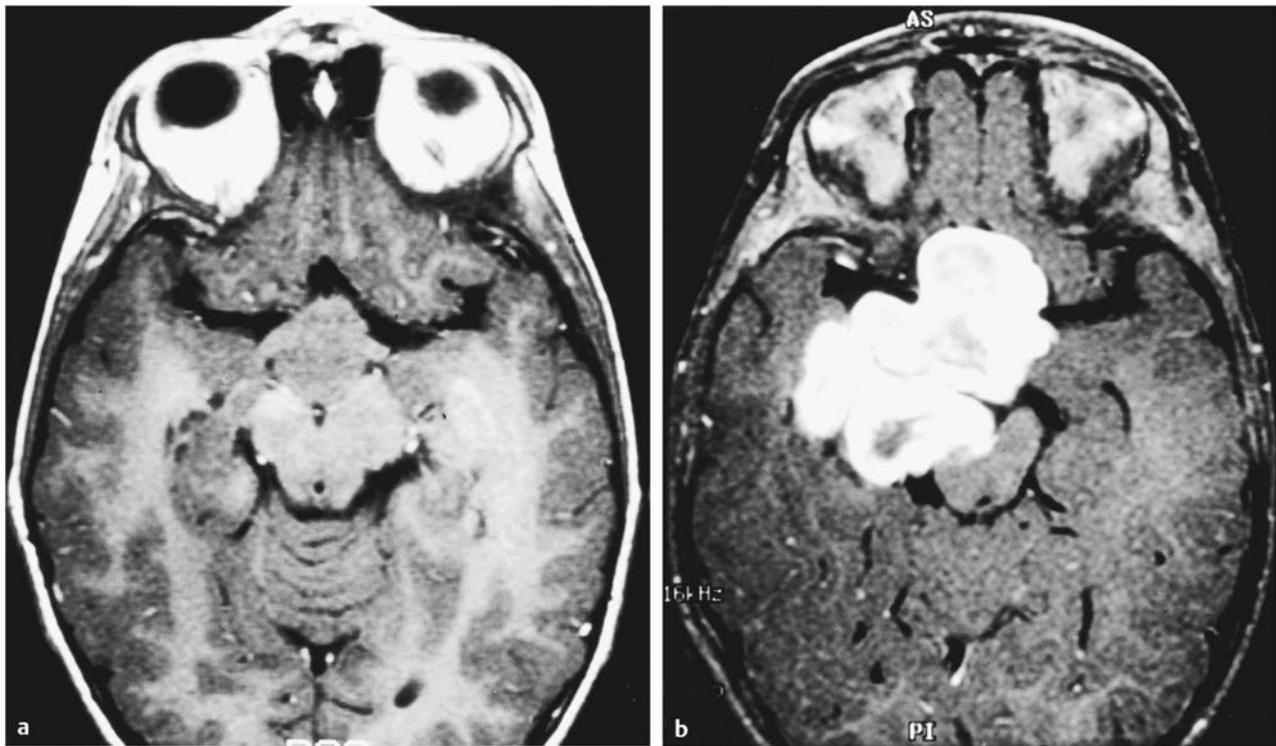


Fig. 48.3 Two magnetic resonance images that illustrate the diverse manifestations of optic–hypothalamic gliomas in patients with neurofibromatosis type 1. (a) Globular enlargement of the optic chiasm is depicted. In this patient, T2 signal abnormality was seen along the optic tracts bilaterally. (b) A massive chiasmatic–hypothalamic glioma shows bright enhancement with intravenous contrast.

the optic nerves and chiasm (► Fig. 48.3a) that may occur in conjunction with T2 signal abnormalities streaking backward along the optic pathways and upward into the hypothalamus. Biopsy of such lesions has generally confirmed the presence of a low-grade glioma.^{41,42} Finally, a small percentage of patients present with a large mass lesion involving the optic chiasm and hypothalamus that may extend upward into the third ventricle, laterally into the temporal fossa, anteriorly beneath the frontal lobe, and posteriorly into the perimesencephalic region (► Fig. 48.3b).

The optimal management for such lesions remains controversial. Before the era of MR imaging and high-resolution computed tomography (CT), optic pathway tumors were generally detected only after the onset of visual impairment, hypothalamic dysfunction, or symptoms of increased intracranial pressure (ICP), which occur in a small percentage of patients and clearly mandate therapeutic intervention. However, most lesions are now detected in asymptomatic individuals in whom the natural history and the indications for intervention are less clear.

Several studies have reported the results of expectant management in patients with NF-1 who had optic pathway tumors that were asymptomatic or minimally symptomatic in association with mild visual loss or precocious puberty.^{41–43} Listernik et al⁴³ noted that only 3 of 33 asymptomatic or minimally symptomatic patients with optic pathway tumors exhibited progressive tumor growth or deteriorating vision after diagnosis, with a median follow-up of 2.4 years. Other groups have also noted that optic gliomas in children with NF-1 have a

distinctly more indolent course than in children without this disorder,^{44,45} although a sizeable subset do progress radiologically and in terms of visual loss.^{46,47} Thus, although the detection of an initially asymptomatic or minimally symptomatic optic pathway lesion on screening MR imaging does not signal the need for immediate intervention, ongoing imaging surveillance is prudent until the natural history can be established conclusively.

However, the role of routine imaging as a screening test remains controversial because most optic pathway lesions in patients with NF-1 are asymptomatic and show a low frequency of significant enlargement, at least in the span of several years.⁴⁸ Several groups have recommended annual MR imaging studies in young children with NF-1. Others have limited imaging to patients with new or progressive symptoms and signs, such as nystagmus, strabismus, visual loss, visual field deficits, precocious puberty, growth delay, diencephalic syndrome, headache, and other symptoms of increased ICP; they recommend following the remaining patients with annual clinical evaluations and ophthalmology examinations.

One drawback to the latter approach is that in children younger than 5 years, deterioration becomes apparent only when impairment is far advanced because objective testing of vision is difficult in these young patients. Accordingly, we often obtain a baseline imaging study in children with NF-1 who are younger than 5 years of age, after which time a thorough ophthalmologic evaluation can generally be performed. Subsequent MR imaging studies are performed only in children with newly diagnosed or progressive visual impairment and in those with

significant abnormalities on initial MR imaging that do not merit immediate treatment, particularly if the children are still too young to cooperate with a thorough ophthalmologic examination. We no longer routinely image older children and instead prefer annual or semiannual clinical evaluations, which include testing of visual acuity and fields as well as a general physical and neurologic examination, with attention directed toward looking for signs of neuroendocrine impairment. The value of visual evoked potential testing for identifying patients with subtle visual impairment from optic gliomas, who may be most likely to benefit from a detailed imaging examination, remains controversial.

However, the aforementioned guidelines do not apply to those children who present with severe visual impairment. In our experience, patients who exhibit significant visual compromise have a high risk for further visual deterioration and require either very close follow-up (e.g., every 3 months) or immediate therapy. These recommendations also do not apply to children who have sizeable, symptomatic lesions on their initial imaging studies because these patients generally require immediate intervention.

Symptomatic optic nerve gliomas in patients with NF-1 have in the past been suggested to have a less favorable prognosis for long-term disease control after surgical resection than comparable lesions in patients without NF-1⁴⁹; however, this probably reflects an artifactual inference in studies conducted in the era before MR imaging, given that a lesion that is truly localized to one optic nerve is uncommon in NF-1 and that unilateral treatment of a bilateral process is unlikely to have long-term efficacy. In more recent studies, symptomatic chiasmatic–hypothalamic tumors in patients with NF-1 actually appear to carry a *more favorable* prognosis for long-term disease control than comparable tumors in patients without NF-1.^{41,42,44,45,50} For example, Hoffman et al⁴¹ noted that whereas only 1 of 23 patients with NF-1 and optic–hypothalamic glioma died of disease progression, 7 of 39 patients without NF-1 died ($p = 0.045$). Deliganis et al⁵⁰ also noted that time to progression among children with newly diagnosed symptomatic optic pathway gliomas arising in association with NF-1 was substantially longer than that for patients with sporadic tumors (8.4 years vs. 2.4 years, respectively). After an average follow-up of 10.2 years, only 5 of 16 patients with NF-1 exhibited disease progression.⁵⁰ In addition, a subset of tumors will exhibit spontaneous regression in the absence of any surgical or adjuvant therapy.⁵¹

With increased understanding of the natural history of optic pathway lesions in patients with NF-1, the indications for surgical intervention have narrowed considerably. Because the histologic identity of a given lesion is rarely in doubt, biopsy for purely diagnostic reasons is generally not needed. In the occasional patient with an optic nerve glioma that is clearly unilateral, in whom proptosis and blindness are apparent, surgical resection of the involved nerve from the globe to the chiasm may be considered. Such cases are rare because the majority of patients are found on MR imaging also to have involvement of the chiasm and contralateral optic nerve. In these children, radiotherapy or chemotherapy, both of which are described in detail below, may be preferable. These patients should also be distinguished from the occasional patient with an orbital plexiform neurofibroma that extends backward from the globe toward the anterior cavernous sinus, in whom radical resection of the

lesion may be required. Surgery has also been advocated for children with large tumors growing exophytically from the optic chiasm.^{41,52} However, it remains uncertain whether the long-term results in terms of disease stability and functional outcome that are achieved with aggressive resection represent an improvement over those obtained with nonsurgical approaches.⁵³

In contrast to the tumors described above, for which surgical intervention may have a role, albeit a controversial one, the majority of optic pathway gliomas are clearly not candidates for excision because of their diffuse involvement of the optic apparatus and hypothalamus. Radiation therapy has historically been used in the treatment of these unresectable lesions, and it provides excellent results in terms of disease stabilization and occasionally regression, often leading to significant improvement in visual function.^{54,55} However, radiation may result in severe cognitive and endocrine deficits^{56,57} and places the patient at risk for radiation-induced malignancies⁵⁸ and vasculopathy, such as moyamoya syndrome.⁵⁹

Accordingly, chemotherapy has come to assume an increasing role in the management of these tumors, particularly in patients younger than 5 to 10 years,^{44,60,61} in whom the risks for long-term radiotherapy-induced cognitive and endocrine impairment are particularly high and in whom the potential benefits of avoiding, or at least deferring, radiotherapy are substantial. A variety of regimens have been employed, with response rates of 20 to 80% and response or stabilization rates of 75 to 100%.^{44,60,61} The efficacy of a carboplatin/vincristine regimen in children with low-grade gliomas associated with NF-1 was recently assessed in detail in the Children's Oncology Group 9952 study, in which the results in terms of disease control appeared to be superior to those in children with low-grade gliomas not related to NF-1.¹⁰⁸ Although children with NF-1 do not appear to differ significantly from those without NF-1 in terms of their response to chemotherapy,⁶⁰ concerns about their potentially increased risk for secondary leukemias resulting from alkylating agents have provided a rationale for avoiding agents like nitrosoureas and temozolomide in front-line regimens. New molecularly targeted agents directed against NF1-related signaling pathway alterations may provide a preferable future alternative for these tumors.

Cerebral and Cerebellar Hemispheric Gliomas

A small percentage of patients with NF-1 develop enlarging lesions within the cerebral (► Fig. 48.4a) and cerebellar (► Fig. 48.4b) hemispheres that differ in appearance from UBOS. The majority of such lesions are gliomas, which exhibit local mass effect and decreased signal on T1-weighted images with enhancement that may be uniform, ringlike, in the form of a mural nodule, or absent altogether. Most lesions are benign and amenable to complete or nearly complete resection, although a small percentage are malignant. Various intraoperative adjuncts, such as stereotactic guidance, intraoperative imaging, and functional monitoring (described more fully in Chapter 34) have allowed resection of deep-seated lesions with acceptable morbidity.

Postoperative management is guided by the histopathologic diagnosis. Low-grade gliomas are managed expectantly after a radiographically complete resection and, in some cases, after extensive subtotal resection. In patients with substantial

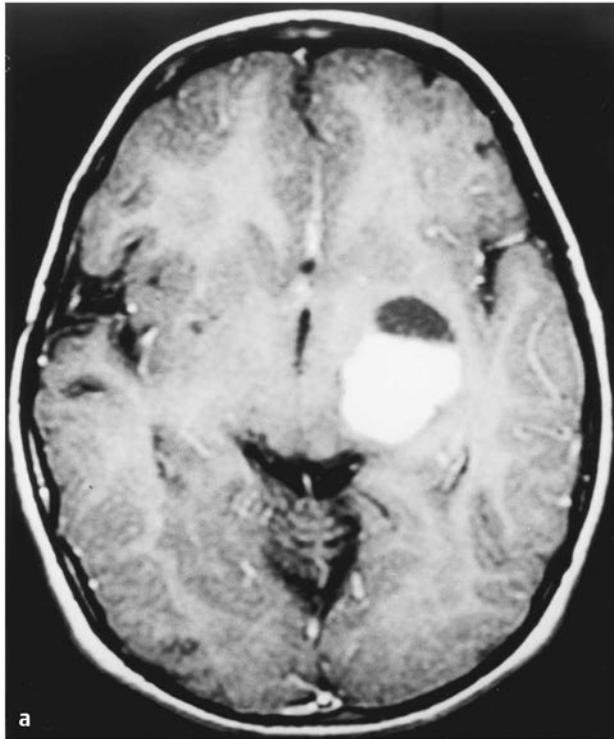


Fig. 48.4 Magnetic resonance images of (a) deep cerebral and (b) cerebellar enhancing lesions in patients with neurofibromatosis 1. Both lesions were detected on follow-up imaging evaluations after the results of initial studies obtained several years earlier had been negative. The patient depicted in (a) had undergone resection of an optic-hypothalamic glioma 8 years previously. Because these lesions had enlarged progressively, complete resection was undertaken. In both cases, low-grade astrocytoma was detected histopathologically.

unresectable disease or those in whom the tumor recurs after an initial resection, adjuvant radiotherapy or chemotherapy is performed as outlined above. In carefully selected patients with well-localized unresectable disease, stereotactic radiosurgery may have a therapeutic role after disease progression.⁶² This approach minimizes exposure of the surrounding brain to radiation, which is an important consideration in patients with NF-1, in whom multiple brain tumors may develop during their lifetime, although we have anecdotally observed an enhanced tendency to radiation swelling in comparison with children who do not have NF-1.

Patients with NF-1 in whom malignant gliomas develop are managed in the same fashion as patients without NF-1, in the absence of any data that these two groups differ prognostically. Specifically, after an attempt at maximal surgical resection, a combination of involved-field radiotherapy and chemotherapy is administered to patients older than 3 years. Younger children are treated with chemotherapy initially in the hope of deferring irradiation for as long as possible. A variety of chemotherapeutic regimens have been studied in cooperative group and limited institution trials, with some evidence of efficacy,⁶³ although the optimal combination of agents remains uncertain. Unfortunately, even with maximal therapy, the majority of affected patients die of progressive disease.

Brainstem Gliomas

Brainstem gliomas in patients with NF-1 are a heterogeneous group that in many ways differ biologically from comparable lesions in patients without NF-1. The most common abnormality is a diffuse area of brainstem enlargement associated with increased signal on T2-weighted images^{38,64} (► Fig. 48.5). Although such lesions have been grouped in some reports with UBOs, their appearance and behavior are distinctive for several reasons. Not only are they substantially larger than typical UBOs, but they also often produce definite mass effect and exhibit abnormal signal on T1-weighted images. Finally, these lesions do not regress over time and are often associated with mild focal neurologic deficits. Their histopathologic basis is problematic. Those tumors that have been biopsied have been found to be low-grade gliomas,⁶⁵ and their generally benign behavior mandates a correspondingly conservative approach to therapy. Thus, although the lesions may in some ways resemble diffuse intrinsic tumors in patients without NF-1, their prognosis generally differs drastically from that of these biologically malignant lesions. Biopsy and adjuvant therapy (or the institution of empiric adjuvant therapy, as is typically done for diffuse brainstem gliomas not associated with NF-1) should be limited to the occasional patient who does show clear clinical and/or

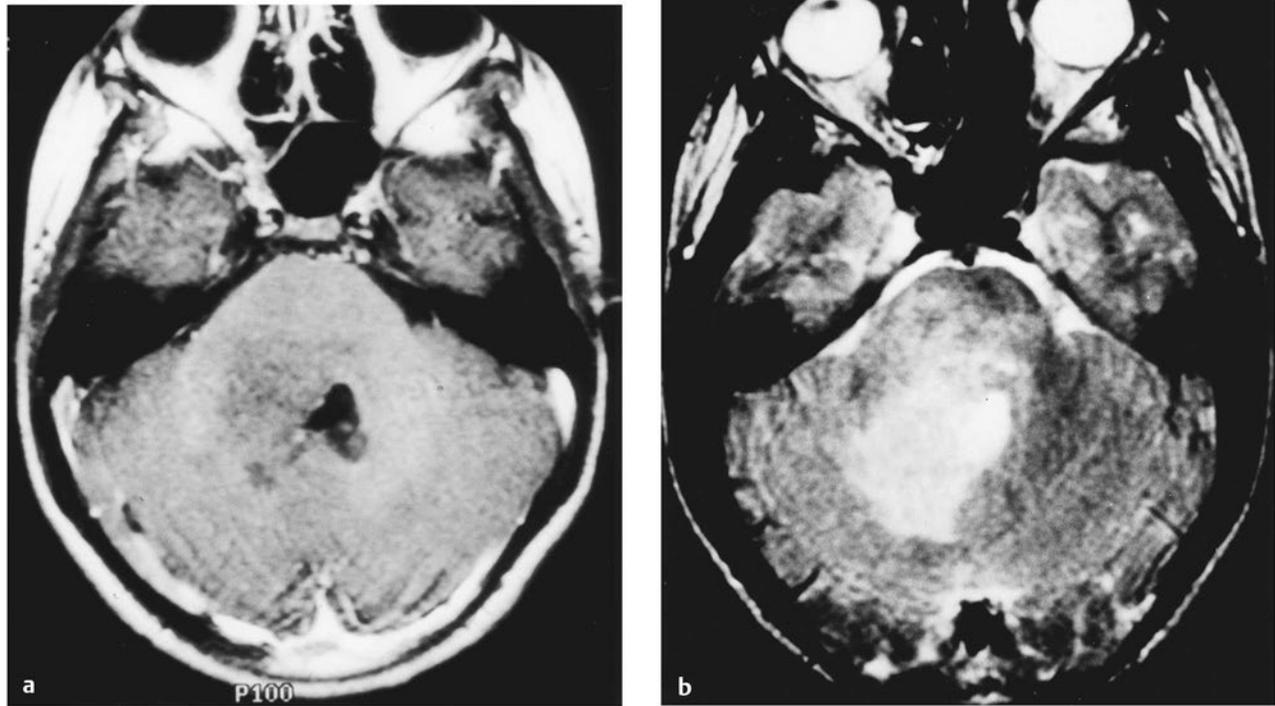


Fig. 48.5 These magnetic resonance images demonstrate a common imaging abnormality in patients with neurofibromatosis 1 (NF-1). The brainstem is diffusely enlarged with (a) decreased T1 signal intensity and (b) increased T2 signal over a wide area centered at the cerebellar peduncle, in some ways resembling the appearance of diffuse intrinsic tumors in patients without NF-1. This patient, shown here at 16 years of age, initially manifested with a right facial paresis and dysarthria secondary to palatal insufficiency at age 4. No imaging evidence of tumor progression was detected during a follow-up interval of 12 years.

radiographic progression.⁶⁶ We do, however, advocate close follow-up imaging of such children until the biological behavior of the lesions can be confirmed because a small percentage will indeed progress.

A second group of brainstem lesions in patients with NF-1 are focal enhancing nodules with or without associated cystic areas.⁶⁴ The biological behavior of these lesions is generally indolent but, ultimately, unpredictable. We have undertaken treatment in those children in whom progressive tumor enlargement was associated with significant local mass effect or with the development of progressive clinical symptoms. Although we have observed small, focal intrinsic lesions to enlarge progressively and asymptotically during adolescence and then regress spontaneously without treatment, exophytic tumors seem to follow a more aggressive course and often require treatment. Such tumors are frequently pilocytic astrocytomas or gangliogliomas, and in some cases they may have anaplastic features. Because the natural history of such lesions remains uncertain, we perform routine follow-up imaging, even in those children who are managed conservatively.

A final group of brainstem lesions in patients with NF-1 are periaqueductal gliomas (► Fig. 48.6). These lesions typically manifest with late-onset aqueductal stenosis and are presumed to be low-grade gliomas, although biopsy confirmation has (appropriately) been limited.^{64,67} The tumors exhibit an indolent course and may remain quiescent for years without intervention, or

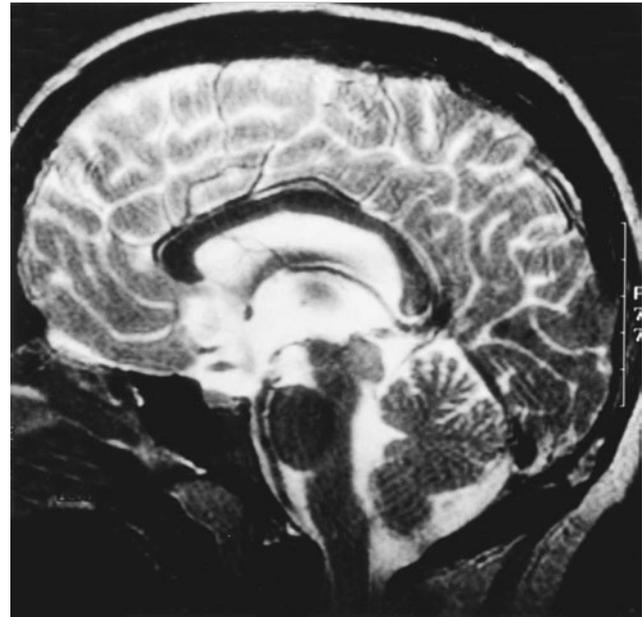


Fig. 48.6 This sagittal T2-weighted magnetic resonance image demonstrates a benign tectal tumor in a child with neurofibromatosis 1 that has remained stable in size for 10 years without specific treatment other than a third ventriculostomy.

they may manifest with obstructive hydrocephalus, in which case treatment with cerebrospinal fluid diversion, ideally third ventriculostomy, is warranted. We typically perform follow-up imaging on a yearly basis for 5 years and periodically thereafter, reserving biopsy and/or adjuvant therapy for lesions that enlarge or produce progressive symptoms.

Neurofibromas

Paraspinal and peripheral neurofibromas are one of the hallmarks of NF-1 and are observed in most patients. These lesions exhibit loss or inactivation of the second *NF1* allele in Schwann cells already harboring an *NF1* mutation or deletion.^{68,69} Although the tumors have been categorized in the past with neurilemmomas, which are the hallmarks of NF-2, the two groups of tumors are readily distinguished on histologic analysis. Neurilemmomas characteristically exhibit alternating areas of cellular (Antoni A) architecture with palisading spindle cells that orient into Verocay bodies and Antoni B architecture comprising a loose array of spindle cells in a mucinous background. In contrast, neurofibromas are composed of spindle cells in a myxomatous stroma that incorporates myelinated and unmyelinated axons, which are rarely seen in neurilemmomas (► Fig. 48.7).

Neurofibromas are best demonstrated on MR imaging, which is useful for delineating the relationship between the tumor, surrounding nerve(s), and adjacent structures. For patients with paraspinal lesions, this study provides information about the extent of foraminal and intraspinal encroachment; for those with visceral lesions, it provides information about the relationship between the tumor and surrounding critical structures. Based on the imaging appearance, the lesions may be categorized by their pattern of growth as fusiform neurofibromas, which are discrete lesions that involve a circumscribed area of a nerve, or plexiform neurofibromas, which exhibit diffuse involvement of a broad extent of one or more nerves.⁷⁰

From a diagnostic and therapeutic standpoint, neurofibromas are often categorized by location as subcutaneous neurofibromas, peripheral nerve neurofibromas, plexus neurofibromas,

paraspinal neurofibromas, craniofacial neurofibromas, or visceral neurofibromas. *Subcutaneous neurofibromas* may occur as isolated, fusiform lesions or as plexiform growths arising from a group of tiny cutaneous nerves. They usually begin as raised subcutaneous masses that may enlarge and become pedunculated over time. Although the tumors may be removed, this is not practical as a rule because new lesions are likely to grow soon. Nonetheless, in selected cases, resection of one or more lesions may be beneficial to the patient's self-esteem, particularly if a cosmetically significant site is involved. Resection is also indicated for lesions that are painful, enlarging rapidly, or arising in an area prone to irritation, such as the belt line. Because a small percentage of these tumors will become malignant, patients should be encouraged to report lesions that enlarge rapidly, become red or ulcerated, or that cause progressive discomfort, because excisional biopsy may be indicated.

Peripheral Nerve Neurofibromas

If symptomatic, peripheral nerve neurofibromas produce neurologic dysfunction in the distribution of a major nerve trunk, with pain and paresthesias that often are initiated or exacerbated by manipulation of the involved nerve (► Fig. 48.8).⁷⁰ Unlike neurilemmomas, which typically involve a single fascicle of a major nerve, with the other fascicles splayed over the tumor capsule, neurofibromas often involve many or all of the fascicles of a nerve. In many cases, this limits their resectability; however, in some instances, it is possible to resect multiple involved fascicles without sacrificing significant neural function. This approach is facilitated by beginning the dissection at the proximal and distal poles of the tumor and identifying the fascicle(s) from which the tumor arises, which may then be sacrificed. Intraoperative nerve stimulation techniques are essential for confirming that the fascicles to be sectioned are indeed non-functional. In some cases, complete resection is not feasible without risking neurologic impairment, and a subtotal resection must be pursued. In these instances, the residual tumor must be followed for evidence of further growth or malignant changes,⁷¹ which often manifest with rapid lesion growth, pain,

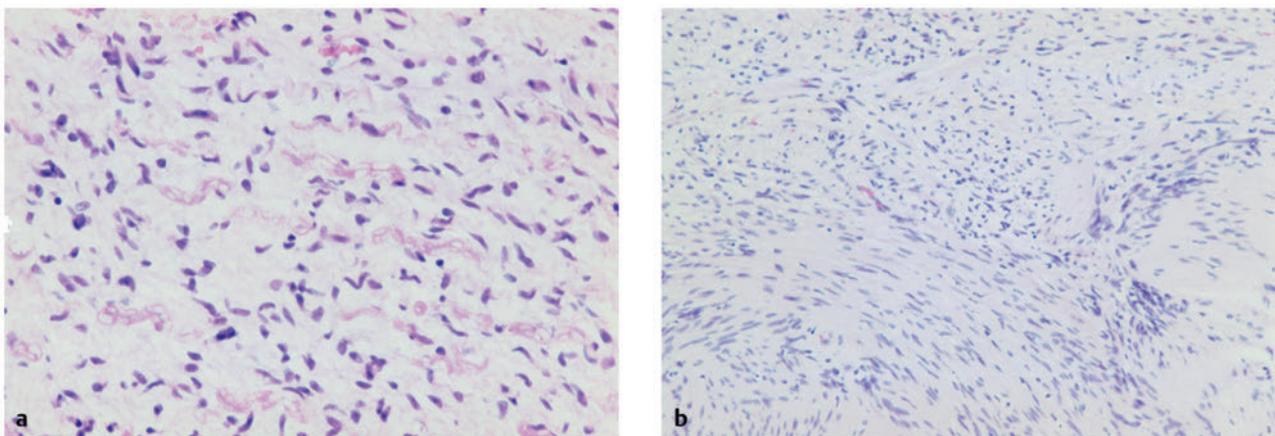


Fig. 48.7 Hematoxylin and eosin--stained paraffin sections of (a) a neurofibroma and (b) a neurilemmoma. Neurofibromas typically exhibit a chaotic array of spindle cells that encompass myelinated and unmyelinated nerve fibers, whereas neurilemmomas characteristically exhibit alternating areas of palisading nuclei and intervening cytoplasm (Verocay bodies) that rarely contains intervening axons.



Fig. 48.8 This magnetic resonance image shows a peripheral neurofibroma in the right median nerve that caused progressive radicular pain and paresthesias exacerbated by direct percussion. The tumor arose from a single fascicle and was amenable to complete resection.

and ulceration. In addition, malignant lesions typically exhibit inhomogeneity and irregular enhancement on MR imaging, whereas benign neurofibromas show uniform enhancement.⁷² For lesions that exhibit malignant features, the operative and postoperative management strategy must involve a multidisciplinary approach incorporating neurosurgical, general surgical, orthopedic, medical oncology, and radiation oncology input.⁷¹

Total resection is inherently infeasible for plexiform tumors, which are nonencapsulated and infiltrate extensively along and within involved nerves. Although en bloc resection and grafting are theoretically possible if only one nerve is involved, the functional results of this approach have been poor. Complete resection is rarely an option for lesions that involve the brachial plexus or lumbosacral plexus, and it is usually reserved for cases with malignancy and those in which pain or compression of surrounding structures leads to intolerable symptoms. Because plexiform lesions may exhibit indolent behavior, aggressive intervention should be limited to tumors causing progressive impairment. Such patients may be appropriate candidates for investigational chemotherapy protocols. Studies of 13-*cis*-retinoic acid, interferon- α , thalidomide, farnesyltransferase inhibitors, and Raf kinase inhibitors have suggested efficacy in terms of stabilizing previously progressive disease, although

objective disease regression is infrequent.^{73,74} The erratic growth of plexiform neurofibromas, as well as their complex geometry, has complicated efforts to establish conclusively that these agents modify the natural history of the tumors.^{75,76} The development of genetically engineered tumor models for NF-1 has provided an opportunity to examine novel therapeutic strategies preclinically, which it is hoped will improve the pace of identifying and prioritizing novel approaches targeted against growth signaling pathways.⁷³

Paraspinal Neurofibromas

Paraspinal neurofibromas are usually fusiform tumors that typically involve nerve roots at their entry into the spinal canal (► Fig. 48.9).⁷⁷ In some cases, virtually every nerve root from the cervical to the sacral spine is involved (► Fig. 48.9a). Because most lesions enlarge slowly, if at all, intervention is reserved for those tumors that show progressive encroachment on the spinal canal with resultant neural compromise (► Fig. 48.9b). These lesions are typically approached with a laminotomy for the intraspinal component. The extraspinal component may be removed transforaminally if the tumor is small and medially located, but larger lesions require a more laterally directed approach. A large extraspinal component of a cervical lesion can be removed with an extreme lateral approach or modifications thereof, with care taken to avoid injury to the vertebral artery.⁷⁸ Thoracic lesions may be removed with a costotransversectomy, lateral extracavitary, or transthoracic intra- or extrapleural approach, depending on the size of the lesion.⁷⁹ Lumbar lesions are usually removed with a retroperitoneal approach, potentially combined with a posterior approach. Resection of the involved nerve root is often required to obtain complete tumor removal; this can sometimes be accomplished without producing severe neurologic impairment, although neuromonitoring techniques are helpful in making this determination and guiding safe resection extent. Because of the aforementioned predisposition of children with NF-1 to the development of scoliosis, patients must be followed with serial clinical and radiographic evaluations for evidence of progressive postoperative deformity,⁸⁰ which is best treated before it reaches an advanced stage.

Craniofacial Neurofibromas

Craniofacial neurofibromas are generally plexiform growths that involve peripheral nerves of the face, orbit, and cranial base. Facial lesions are generally treated by plastic surgeons; the major neurologic issue is the potential for facial or trigeminal nerve compromise resulting from compression by the tumor or injury during tumor resection. Orbital lesions present a major cosmetic and functional challenge because they often produce proptosis, strabismus, and visual compromise. These lesions can also extend intracranially into the cavernous sinus and are rarely resected completely without sacrificing the globe; hence, surgery is reserved for patients with advanced visual loss and unremitting tumor growth.⁸¹ In patients with intact vision, functional stabilization can often be achieved by partial tumor resection because the residual lesion will sometimes fail to grow.

Visceral Neurofibromas

Visceral neurofibromas (► Fig. 48.10) also constitute a challenging management problem because they are usually plexiform

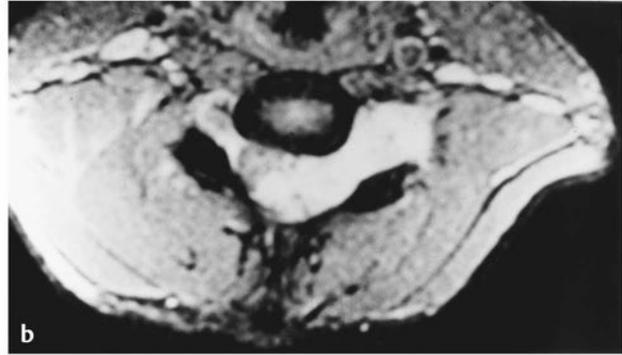


Fig. 48.9 Magnetic resonance images. (a) Multisegmental involvement of the exiting spinal nerve roots by neurofibromas in an 11-year-old boy. These lesions caused no intraspinal compression and have remained stable for more than 8 years without intervention. (b) Intraspinal growth of one of several paraspinal neurofibromas in an 18-year-old boy caused a mild, progressive Brown-Séquard syndrome. This lesion was resected completely, and the patient remains free of disease progression.



Fig. 48.10 Magnetic resonance image of a rapidly enlarging plexiform neurofibroma in a 7-year-old girl involving the left brachial plexus, thoracic cavity, and parapharyngeal region from the chest to the skull base, producing moderate tracheal compression and enveloping the great vessels of the neck. The patient presented with myelopathy and radiculopathy from an associated intraspinal tumor component, which was resected. The extraspinal component stabilized after the initiation of chemotherapy with interferon- α .

tumors that cannot be completely removed and pose a long-term risk for progressive impairment and malignant transformation. Subtotal resection is often indicated to relieve pulmonary compromise (from large intrathoracic lesions), upper airway obstruction (from parapharyngeal neurofibromas), abdominal discomfort, or spinal cord compression (from foraminal encroachment of a paravertebral tumor). Like other unresectable plexiform neurofibromas, these tumors are appropriate candidates for chemotherapy trials.

Neurofibromatosis 2

Vestibular Neurilemmomas

Tumors of the eighth cranial nerve occur in most patients with NF-2 and often become symptomatic in adulthood, where they are beyond the scope of pediatric neurosurgical practice. However, occasional lesions are detected earlier in childhood (► Fig. 48.11), particularly as a consequence of advances in neuroimaging coupled with the proactive screening of children of affected adults.^{18,82} The finding in a child of a posterior cataract or multiple spinal cord or peripheral nerve tumors, without Lisch nodules, café au lait macules, or an alternative explanation, should raise concern about an underlying diagnosis of NF-2, and such children should undergo an MR imaging examination of the head for intracranial manifestations of NF-2. The development of symptomatic tumors in childhood tends to indicate a more aggressive course in comparison with that of older patients who have this disorder.⁸³⁻⁸⁵

Although there is general agreement that MR imaging is the optimal screening tool for vestibular neurilemmomas in

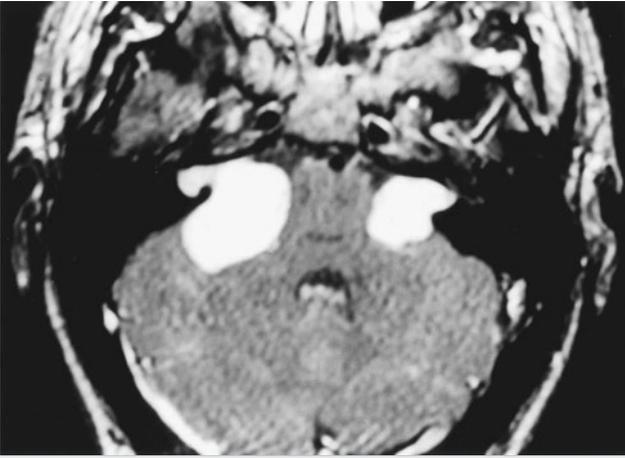


Fig. 48.11 Magnetic resonance image of bilateral vestibular neurilemmomas in the 16-year-old son of a woman with known neurofibromatosis 2. On initial examination, he was noted to have unilateral blindness from a posterior cataract and right-sided deafness that reportedly had developed insidiously. The larger, right-sided vestibular lesion was resected uneventfully, and the left-sided lesion was observed while the patient learned sign language and lip reading.



Fig. 48.12 Magnetic resonance image of a foramen magnum meningioma in a child with neurofibromatosis 2 that manifested with neck pain and ataxia; the lesion was completely resected.

individuals at risk for NF-2 and that periodic hearing tests are indicated for the functional evaluation of these patients, the indications and preferred approaches for the treatment of these lesions, once detected, remain controversial. Their natural history is variable, although the majority of patients will show progressive tumor enlargement and hearing deterioration over time, which can be apparent even between annual evaluations and may differ between the two ears in patients with bilateral lesions.⁸⁶ The primary management goal is the preservation of function, but the best way for achieving this outcome is uncertain. In a patient with a large lesion causing significant brainstem compression, the decision to proceed with surgical resection is relatively clear. However, for patients with relatively small, asymptomatic lesions, the optimal approach is less obvious. Some surgeons recommend early attempts at radical tumor resection based on the view that this approach has the greatest likelihood for preserving hearing postoperatively.^{87,88} However, the risks for iatrogenic hearing loss are all “up front” and pose a major concern in a patient with functional hearing in whom tumor- or treatment-induced deafness in the contralateral ear is a significant long-term risk. Among those who favor early surgery, some recommend removing the larger of two lesions, with the thought that this lesion is most likely to pose an initial threat of ipsilateral hearing loss. Others, however, advocate removing the smaller lesion, which theoretically affords the patient the best chance of achieving both tumor removal and ipsilateral hearing preservation. Tumor resection is sometimes combined with placement of a cochlear or auditory brainstem implant, which may provide a way for ensuring at least some hearing preservation in patients with bilateral tumors who undergo surgical intervention.^{89,90}

However, an equally cogent argument can be made for deferring surgery until there is objective evidence of tumor progression or hearing loss. Because of the variable natural history of these lesions, the detection of bilateral vestibular nerve tumors in a patient with NF-2 does not necessarily imply that either lesion is going to immediately threaten hearing.^{19,91} Stereotactic radiosurgery provides an alternative approach for the treatment of such lesions.^{92,93} It is uncertain whether the chances for long-term hearing preservation are any better than with open resection; however, hearing loss, if it occurs after radiosurgery, typically develops in a delayed fashion. This interval provides the patient time to learn sign language and lip reading. Another approach that has been advocated in patients with bilateral tumors is subcapsular resection of the lesion, leaving a small amount of tumor adherent to the facial and acoustic nerves to minimize the risk for nerve injury.⁹⁴ In the absence of objective data to support one management approach versus another, we believe that therapeutic decision making should be individualized, with the risk tolerance of the patient and family taken into account, after the various management approaches with their pros and cons have been thoroughly discussed. Because of the complexity of the management issues involved, a supraregional approach to the care of affected patients has been advocated to optimize functional outcome.⁹⁵ More recently, pharmacologic approaches have been explored for these tumors, particularly bevacizumab, which has demonstrated tumor regression, although the applicability of this agent for long-term disease control remains to be defined.⁹⁶⁻⁹⁸

Intracranial Meningiomas and Nonvestibular Cranial Nerve Neurilemmomas

More than 30% of patients with NF-2 have multiple nonvestibular neurilemmomas, and approximately half have meningiomas (► Fig. 48.12).^{82,99} For reasons that are unclear, symptomatic meningiomas in these young patients follow a more aggressive course than do those arising in adults with NF-2.¹⁰⁰ It has been suggested that a distinct subgroup of patients with NF-2 are at highest risk for multicentric intracranial neurilemmomas and meningiomas.^{99,101} Not all of the phenotypic heterogeneity, however, is explained by inherited differences in the pattern of *NF2* mutations because variable patterns of tumor growth have been noted among patients with identical mutations and even among identical twins.¹⁰² The latter observation has important implications for the screening of patients with NF-2. Presently, it is impossible to predict which patients will develop multiple intracranial tumors, and in the absence of a conclusive genotype–phenotype correlation, periodic cranial neuroimaging is advocated in all affected patients. Occasionally, patients with NF-2 will initially present with seizures from meningioangiomas, which is a hamartomatous proliferation of capillary-size vessels, meningothelial cells, and fibroblasts within the cerebral cortex. It may occur with or without concurrent meningioma formation.¹⁰³

From a therapeutic standpoint, many of the above comments regarding vestibular neurilemmomas apply to other intracranial neurilemmomas and meningiomas. These lesions exhibit unpredictable biological behavior; some tumors remain quiescent for extended intervals, whereas others enlarge rapidly, necessitating vigilant imaging and clinical follow-up. Because affected patients will often develop multiple intracranial neurilemmomas and meningiomas, we generally reserve operative intervention for those who have lesions that cause obvious neural compression or that exhibit progressive growth.

Intraparenchymal Gliomas

Patients with NF-2 may develop intrinsic glial neoplasms of the brain, but such lesions are less commonly seen than in patients with NF-1. In contrast, intraspinal intramedullary tumors are more common in patients with NF-2.^{21,82,104,105} In such patients, ependymomas are more frequent than astrocytomas, whereas the converse is observed in patients with NF-1.¹⁰⁶ Because ependymomas are generally well circumscribed, complete resection is often feasible and is indicated for lesions that are large and those that show definite signs of progression.^{21,106}

Extracranial Neurilemmomas and Meningiomas

A significant percentage of patients with NF-2 exhibit intraspinal growth of nerve sheath tumors and meningiomas (► Fig. 48.12).^{82,105} Because these tumors grow slowly and displace rather than invade the surrounding neural structures, impressively large lesions may be asymptomatic for years



Fig. 48.13 Magnetic resonance image of an 18-year-old male with multisegmental intraspinal tumors causing progressive myelopathy. Three discrete lesions of the cervical and thoracic regions were removed; two proved to be meningiomas and one was a neurilemmoma.

before cord compromise is clinically apparent. We generally favor tumor resection for patients with radiographic evidence of pronounced cord compression, even in the absence of symptoms. Because the nerve sheath tumors in NF-2 are usually neurilemmomas¹⁰⁷ rather than neurofibromas, extracranial lesions are generally well circumscribed and arise from a single nerve fascicle, which often can be sacrificed with minimal neurologic morbidity.⁷⁰ In general, meningiomas can be removed without

resecting any neural elements. A small percentage of patients have neurofibromas, which pose the same difficulties as those arising in the context of NF-1.⁸² In some instances, patients will require the removal of several lesions at different levels because of profound multisegmental cord compression (► Fig. 48.13).^{82,99,105} Our observation has been that children who exhibit intact neurologic function preoperatively maintain this during the postoperative period and many patients with deficits improve, whereas those with profound impairment usually fail to recover, which supports the concept of early surgery. However, we do not routinely remove lesions that are producing little or no spinal cord compression and, instead, follow these patients periodically with clinical evaluations and MR imaging examinations of the spine.

48.3 Counseling

Beyond the acute evaluation and management of specific medical and surgical problems that arise in patients with NF-1 and NF-2, there are issues related to having a genetic disorder, especially a chronic one affecting multiple systems, that are best addressed by a clinical geneticist or genetic counselor. This person clarifies inheritance risks in terms understandable to the patient or parents. The family may wish to learn about technical details regarding reproductive options to avoid having additional children with NF, including prenatal diagnosis, gene testing, and assisted reproductive procedures. Because gene testing is now commercially available, the pros and cons of undergoing DNA analysis of the genes for NF-1 and NF-2 need to be the subject of extended discussion. The geneticist also offers anticipatory guidance and conducts or expedites diagnostic examinations for other family members who, by their position in the family tree, may be at risk for NF.

Because patients and families affected by NF-1 and NF-2 are faced with a lifetime of uncertainty regarding the natural history of the disorder, which may be superimposed on chronic difficulties in learning and socialization (in NF-1) and cosmetic concerns (in both disorders), social services or psychological support is often beneficial. Finally, local support groups, often affiliated with one of the national organizations in the United States, such as the National Neurofibromatosis Foundation (<http://www.nf.org>), the Children's Tumor Foundation (<http://www.ctf.org>), and the Neurofibromatosis Network (<http://nfnetwork.org>), provide patients and families with an opportunity to share their experiences with others and keep abreast of new developments in the field. Finally, a geneticist, neurologist, or knowledgeable generalist, such as a family practitioner, pediatrician, or internist, should monitor the patient according to published guidelines for health supervision,²⁷ to complement the periodic comprehensive evaluations that are provided by a multidisciplinary NF clinic.

Pearls

- Because NF-1 and NF-2 are multisystem disorders, patients often present with symptoms and signs not directly referable to a central nervous system tumor. Recognition of the significance of these findings and knowledge of the indications for intervention are essential for optimizing outcome. The complexity of the diagnostic and management decisions that arise in children with NF-1 and NF-2 support the use of a multidisciplinary approach to patient management.
- By far the most commonly detected abnormalities on MR imaging in children with NF-1 are foci of increased signal on T2-weighted images without T1 signal change or mass effect. Because these lesions typically follow a benign course, their management must be conservative.
- The management of children with NF-1 and optic pathway tumors must be individualized because the natural history of these lesions varies widely.
- Although optic gliomas and intrinsic brainstem gliomas in children with NF-1 seem to differ biologically from similar-appearing lesions in patients without NF-1, cerebral and cerebellar hemispheric gliomas and exophytic brainstem gliomas in patients with NF-1 should be managed according to the same guidelines used for patients without NF-1.
- The majority of peripheral nerve tumors in patients with NF-1 are neurofibromas, whereas those in patients with NF-2 are neurilemmomas. Although isolated neurofibromas may be amenable to complete resection, plexiform lesions can rarely be completely removed without unacceptable morbidity. Neurilemmomas are usually amenable to complete resection.
- Because patients with NF-1 and NF-2 may have multiple central nervous system tumors, intervention is usually reserved for lesions that cause or are highly likely to cause, progressive neurologic dysfunction and for those that show relentless growth.

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49 The Phakomatoses

Robert P. Naftel and Ian F. Pollack

The term *phakomatosis* was first coined by ophthalmologist Jan van der Hoeve in 1920 to compare similarities between neurofibromatosis and tuberous sclerosis.¹ In doing so, he defined the term *phakoma* to describe congenital tumors in multiple tissues distinct from nevi by the lack of nevus cells.² When he coined the term, strict inclusion or exclusion criteria for this category were omitted. Over time, because of this looseness of definition, many conditions have been included in the category. Another popular term for these conditions is *neurocutaneous disorders*.

The syndromes that are covered in this chapter are the more common phakomatoses, as well as the conditions that are the most relevant to neurosurgeons. They include tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau syndrome, hereditary hemorrhagic telangiectasia, basal cell nevus syndrome, and neurocutaneous melanosis. Neurofibromatosis is discussed in a separate chapter but is a member of this group. Other syndromes that could be included in this category are ataxia telangiectasia, incontinentia pigmenti, and Wyburn-Mason syndrome.

49.1 Tuberous Sclerosis Complex

49.1.1 Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder with variable penetrance that causes multiple-organ dysfunction. Tumors can form in the brain, kidneys, heart, eyes, lungs, and skin. In 1862, the constellation of findings was first noted by von Reckinghausen.³ However, the disorder did not receive its name until Magloire Bourneville applied the term *sclérose tubéreuse* to describe the gross appearance of the autopsy findings.⁴ The disorder is relevant to neurosurgeons because 85% of children have neurologic sequelae, including epilepsy, tumors, and behavioral and psychological problems.⁵

49.1.2 Epidemiology

From 1 in 6,000 to 1 in 14,000 children younger than age 10 are estimated to have TSC,^{6,7} but the prevalence may be higher because of the variable severity of disease expression.⁸ When the difference in expression is accounted for, the birth incidence is estimated to be 1 in 5,800.⁹ There are no known demographic categories that are predominantly affected.

49.1.3 Clinical Presentation

The most common cutaneous finding is hypopigmented macules, also known as ash leaf spots, which are present in 90 to 98% of patients with TSC patients versus only 4.7% of the general population (► Fig. 49.1).^{5,10,11} These lesions are most easily detected with a Woods lamp and are often located on the trunk or buttocks.¹¹ Bilateral facial angiofibromas (also known as adenoma sebaceum), which form a butterfly pattern over the bridge of the nose and malar eminences, are present in 80% of

children with TSC who are older than 5 years (► Fig. 49.2).¹¹ Shagreen patches, present in 54% of patients older than 5 years, are connective tissue nevi found commonly on the lumbosacral flanks or dispersed over the trunk and thighs.¹² Forehead fibrous plaques are another type of angiofibroma found in about 36% and may be present at birth.¹² Periungual fibromas (also known as Koenen tumors), which usually do not develop until age 15 to 29, are more common in women and preferentially form on toes. Molluscum fibrosum pendulum (also known as a skin tag) is commonly found in adults and is located on the neck, groin, axillae, and flexor surfaces of limbs.¹¹ Dental pits are present in 90% of patients with TSC, whereas they are present in only 9% of the general population.¹³

Cardiac rhabdomyomas, an almost exclusively pediatric manifestation of TSC, are a primary finding in fetuses and infants. Of infants with cardiac rhabdomyomas, 96% are diagnosed with TSC.¹⁴ Generally, these lesions are asymptomatic and detected on fetal ultrasound or when a murmur is present. Occasionally, they can be large enough to cause cardiac output dysfunction or significant arrhythmias. These tumors regress throughout early childhood, with the most dramatic reduction occurring during the first 3 years of life.^{15,16}



Fig. 49.1 An 8-year-old boy with hypopigmented macules (also known as ash leaf spots). These lesions are most often located on the trunk or buttocks.



Fig. 49.2 An 11-year-old boy with bilateral facial angiofibromas (also known as adenoma sebaceum), which form a butterfly pattern over the bridge of his nose and malar eminences.

Kidney complications are the most common tuberous sclerosis-related cause of death.¹⁷ The renal manifestations include renal angiomyolipomas, renal cysts, and renal cell carcinoma (RCC). Although renal angiomyolipomas are predominantly present in adults, up to 16% of children younger than 2 years old can be affected and may require treatment, either through embolization or surgical resection.^{18,19} Renal cysts may be present but are usually asymptomatic. RCC is present in 2 to 3% of patients with TSC and is usually diagnosed during childhood.²⁰

Although extremely rare in pediatric TSC, pulmonary lymphangiomatosis is a progressive disease process that begins with shortness of breath, cough, and chest pain. It can be very difficult to treat.²¹

On ophthalmologic examination, retinal hamartomas are found in 40 to 50% of patients. These hamartomas have variable morphological appearances but rarely affect vision.²²

Neurologic sequelae of TSC include epilepsy, neoplasms, hydrocephalus, and neurocognitive or behavioral dysfunction. On magnetic resonance (MR) imaging, affected patients typically exhibit multiple characteristic structural abnormalities, including cortical tubers, which may or may not be calcified; subependymal nodules, which do not enhance; and subependymal giant cell astrocytomas (SEGAs), which are enhancing, noncalcified lesions near the foramen of Monro (► Fig. 49.3). These lesions contribute to the neurologic manifestations listed above.⁷ The tubers can be located anywhere in the cortex; however, they are most commonly located in the frontal and parietal lobes. They represent focal areas of cortical dysplasia and appear as expanded gyri with high intensity on all MR imaging sequences (► Fig. 49.4). Tubers do not generally enhance with contrast. Subependymal nodules have the appearance of periventricular “candle drippings” that do not enhance.²³

Epilepsy is associated with the cortical tubers; however, it is not clear whether the tubers themselves or the perituberal cortex is epileptogenic.^{24,25} The prevalence of epilepsy in TSC is reported to be 80 to 90%.⁹ In children who develop epilepsy, seizures typically begin in the first year of life, and 85% of cases will be refractory to medical treatment. Usually, the seizures are focal at first; however, they can be preceded by or progress

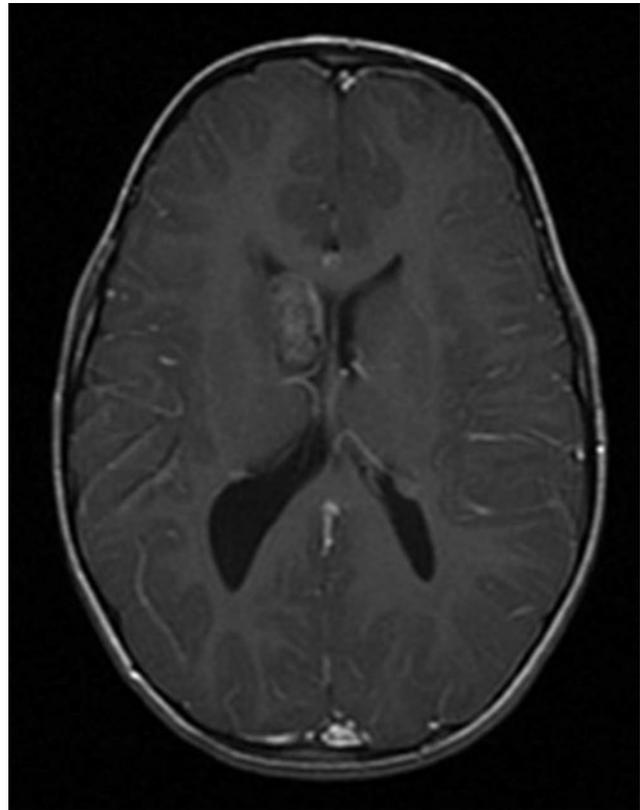


Fig. 49.3 Magnetic resonance imaging of the brain of a 4-year-old girl with tuberous sclerosis complex. This axial T1-with-contrast sequence demonstrates a subependymal giant cell astrocytoma, which is an enhancing, noncalcified lesion near the foramen of Monro.

to infantile spasms. Infantile spasms usually evolve into other types of seizures, oftentimes leaving children with multiple seizure types.²⁶ These children are at an increased risk for developing neurocognitive disabilities.²⁷ Generally, children with *TSC2* genetic mutations are at higher risk for developing more severe seizure phenotypes.²⁸

SEGAs are tumors near the midline in close proximity to the foramen of Monro that develop in 5 to 15% of patients with TSC.^{29,30} They most commonly occur in the first two decades of life; the mean age at presentation is 11 years.³¹ SEGAs grow slowly and are generally 2 to 3 cm at the time of diagnosis. As World Health Organization (WHO) grade I tumors, they generally cause symptoms from mass effect, either through hydrocephalus or direct compression of the deep nuclei.³² On imaging, they can be difficult to differentiate from subependymal nodules. However, if a lesion is larger than 12 mm, enhances, and is near the foramen of Monro, it is likely an SEGA.³³

Neurocognitive function varies from nearly normal to severely disabled, the latter often reflecting autistic or other neurobehavioral disorders. About 30% of children are extremely impaired, without the ability to live an independent life. However, 50% may have a normal IQ but still have some cognitive deficits.³⁴ There are high rates of autism associated with TSC.^{35,36} Poor cognitive outcomes have been linked to intractable seizures, *TSC2* mutation, and the location of cortical tubers.³⁷

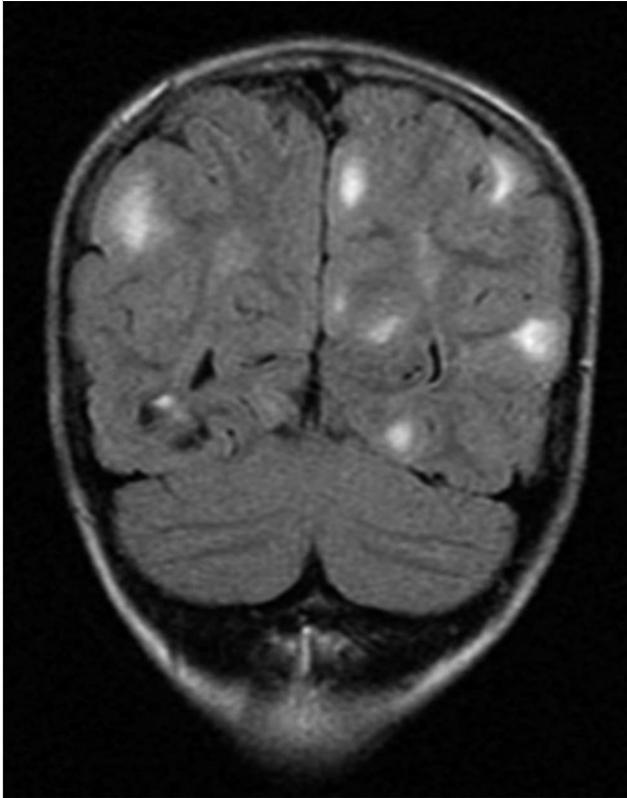


Fig. 49.4 Magnetic resonance (MR) imaging of the brain of a 4-year-old girl with tuberous sclerosis complex. This coronal fluid-attenuated inversion recovery (FLAIR) sequence demonstrates tubers, which represent focal areas of cortical dysplasia and appear as expanded gyri with high intensity on all MR imaging sequences. Tubers do not generally enhance with contrast.

49.1.4 Pathology and Genetics

TSC is an autosomal-dominant inherited disorder. However, nearly two-thirds of cases are believed to result from sporadic mutations.^{9,38} The mutations have been identified as affecting two tumor suppressor genes, tuberous sclerosis complex 1 (*TSC1*), and tuberous sclerosis complex 2 (*TSC2*), and have been mapped to chromosomes 9q34 and 16p13.3, respectively.^{39,40} Of the sporadic mutations, *TSC2* mutations are the most common, responsible for 75 to 80% of cases.⁴¹ *TSC1* and *TSC2* encode the proteins hamartin and tuberin, respectively. Under normal conditions, the proteins act as a dimer that activates a guanine triphosphatase (GTPase). This acts as a negative downstream regulator of the mammalian target of rapamycin (mTOR), which has been the therapeutic target of rapamycin and similar drugs.⁴² Dysregulated mTOR activation has been implicated in the development of SEGAs and of cortical dysgenesis.⁴³ Patients with the same genotype, even within a family, can exhibit very different phenotypes. Although there are exceptions, generally *TSC2* mutations have more severe clinical manifestations than *TSC1* mutations.^{41,44}

49.1.5 Diagnostic Studies

A consensus conference defined criteria for the diagnosis of TSC. These criteria include major and minor features, and the

diagnosis is made when a patient exhibits two major or one major and two minor features. The features include clinical signs and radiologic findings that are specific for tuberous sclerosis.⁴⁵ These diagnostic criteria do not include genetic testing. Genetic testing is informative if the results are positive; however, it detects only 85 to 90% of *TSC* mutations, which is considered a relatively low sensitivity.⁴⁶

When a child is diagnosed with TSC, many diagnostic studies are needed to assess the degree of systemic involvement (see box “Tuberous Sclerosis Management (p.644)”⁷). Throughout childhood, the patient undergoes surveillance monitoring to identify the frequent complications of TSC that are treatable if diagnosed early but are highly likely to cause morbidity or mortality if the diagnosis is delayed (see box “Tuberous Sclerosis Management (p.644)”⁷). Therefore, testing is directed toward diagnosing renal angiomyolipomas, SEGAs, cardiac rhabdomyomas, and pulmonary lymphangiomyolipomas, because these are the major causes of premature mortality in TSC.^{7,17} Any of these evaluations should be repeated more frequently when clinically indicated.⁷

Tuberous Sclerosis Management

- Initial evaluation
 - Magnetic resonance (MR) imaging of the brain with and without contrast
 - Electroencephalography (EEG; less essential in older children who are developmentally normal and without seizures at the time of diagnosis)
 - Neurodevelopmental testing
 - Electrocardiography to evaluate for arrhythmias
 - Echocardiography if there are arrhythmias or cardiac dysfunction
 - Renal ultrasound
 - Ophthalmologic examination
 - Dermatologic examination for concerning cutaneous manifestations
- Surveillance
 - MR imaging of the brain every 1 to 3 years
 - Renal ultrasound every 1 to 3 years
 - Neurodevelopmental testing repeated at school entry
 - Repeated electrocardiography, echocardiography, EEG, ophthalmologic evaluation, and dermatologic evaluation as clinically indicated

Data from Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;372(9639):657–668.⁷

49.1.6 Treatment

A multidisciplinary approach is required to manage patients with TSC. The treatment of the nonneurosurgical features of TSC is beyond the scope of this chapter, but patients should undergo the previously described surveillance testing and be treated as needed by the appropriate medical specialists.⁷

Traditionally, surgery has been the treatment of choice for SEGAs, and it is curative with complete resection.³³ These tumors are usually resected through a transcallosal or transcortical approach; however, authors have described purely endoscopic

approaches.⁴⁷ When complete resection cannot be achieved, patients typically experience slow growth of the tumor residual that requires further treatment.⁴⁸ Gamma Knife has been used as both primary and adjuvant treatment; however, the results have not been consistently promising.^{49,50} Recent breakthroughs in pharmacologic therapy for SEGAs have taken advantage of mTOR pathway inhibition and have used rapamycin (sirolimus), its prodrug CCI-779 (temsirolimus), or its analogue RAD001 (everolimus) to counteract the uncontrolled mTOR pathway.³¹ These drugs are still currently being investigated, but it is notable that significant reduction in tumor size occurred in the majority of patients; however, the reduction was not durable after the cessation of treatment.⁵¹⁻⁵³ The exact role of mTOR inhibitors is still being established through ongoing clinical trials. It is likely that there are clinical scenarios that will be managed by using mTOR inhibitors as either neoadjuvant therapy or for residual or surgically inaccessible lesions.³¹

Despite the use of multiple antiepileptic drugs (AEDs), many children develop intractable epilepsy.²⁶ These patients are candidates for surgical evaluation for resection of the primary epilepsy focus or, in some cases, insertion of a vagal nerve stimulator. Another option is a ketogenic diet.⁵⁴ For the treatment of infantile spasms, vigabatrin is the first-line therapy, even though there can be significant ophthalmologic complications.⁵⁵ Second-line therapy includes corticosteroids or other AEDs. For infantile spasms, surgery can be an option if the infantile spasms are believed to be generated by a focal lesion.⁵⁶ For focal seizures, vigabatrin is recommended if the child is younger than 1 year; other AEDs are used if the patient is older than 1 year. Surgery should be considered early as a second-line therapy if the seizures are refractory to AEDs and the patient has a surgically resectable localized lesion.⁵⁶ Third-line therapy would be vagal nerve stimulation or a ketogenic diet.^{54,56,57}

Patients for whom surgery is being considered should proceed through the usual epilepsy surgical evaluation, which may differ slightly among centers but includes noninvasive video electroencephalography (EEG), MR imaging, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), and neurocognitive testing. In many cases, the evaluation leads to invasive monitoring with subdural and depth electrodes.⁵⁶ Sometimes, a multistage operation is required for a patient with multiple epileptogenic foci.⁵⁸

Despite these epilepsy treatment options, up to one-third of patients remain resistant to treatment. Current investigations are examining the role of mTOR inhibitors for epilepsy, in parallel with the use of these agents for the treatment of SEGAs.⁴³ In studies of mTOR inhibitors for the treatment of SEGAs, patients were noted to have a reduction in seizure frequency.⁵³ The potential of using mTOR inhibitors to treat epilepsy is offset by the probable need for long-term therapy and potential side effects or toxicity profile, as well as the complexity of enzyme upregulation that occurs with many AEDs.

49.1.7 Prognosis

Early death in patients with TSC is most often caused by complications of renal disease.¹⁷ Early death can also be due to status epilepticus or hydrocephalus secondary to SEGAs.³⁰

49.2 Sturge-Weber Syndrome

49.2.1 Introduction

Sturge-Weber syndrome (SWS), also known as encephalotrigeminal angiomas, is a sporadic congenital disorder affecting the brain, face, and eyes.⁵⁹ In 1879, William Sturge first described the clinical syndrome,⁶⁰ and in 1922, Frederick Weber described the radiographic findings as well as the pathophysiologic vascular steal phenomenon.⁶¹ Unlike most other phakomatoses, SWS is not inherited and is not associated with neoplasms; however, SWS is relevant to neurosurgeons because of the prevalence of intractable epilepsy and the potential need for epilepsy surgery.⁶²

The syndrome consists of multiple clinical and radiologic findings, including a facial port-wine stain (PWS), leptomeningeal angiomas, angiomas of the choroid plexus, and congenital glaucoma. Three variants of SWS have been described, spanning a spectrum of disease severity. Type 1 is the traditionally described SWS, with the facial PWS, leptomeningeal angiomas, choroid angioma, and congenital glaucoma. Type 2 is the PWS alone without intracranial involvement. Lastly, type 3 is exclusively leptomeningeal angiomas and occurs in about 10% of cases.^{63,64}

49.2.2 Epidemiology

The prevalence is estimated to be 1 in 50,000 live births. No gender or racial predilection exists.⁶⁵

49.2.3 Clinical Presentation

The clinical manifestations vary in severity among patients and can progress over time. Typically at birth, patients with SWS exhibit a PWS, which is a facial capillary malformation.⁵⁹ This facial stigma can have variable appearances, including that of a salmon patch; however, throughout this chapter, it is referred to as a PWS. Most often, a PWS is located in the V₁ distribution of the trigeminal nerve, but it can extend into the V₂ or less commonly the V₃ distribution.^{59,66,67} In up to 10% of patients, the PWS can be bilateral (► Fig. 49.5).⁶⁸

Leptomeningeal angiomas develops in only 8 to 20% of children born with a PWS. The presence of leptomeningeal angiomas is more likely when the PWS is in the V₁ distribution, large, or bilateral.⁶⁶⁻⁶⁸ If the PWS is unilateral, then any leptomeningeal angiomas is generally ipsilateral. The parietal and occipital lobes are the most common location for leptomeningeal angiomas, but it can cover an entire hemisphere or be bilateral.⁶⁹

Epilepsy, developmental delay, cognitive deficits, headaches, spastic hemiparesis, and cerebral ischemia with transient ischemic attacks and strokes can occur.⁷⁰⁻⁷³ Seizures occur in nearly 75% of patients with unilateral disease and in 95% of those with bilateral disease.^{69,71} They begin at a median age of 6 months; among 75% of patients with SWS in whom epilepsy develops, seizures begin in the first year of life.^{72,73} Intractable epilepsy is associated with seizures beginning in the first year of life, but much of the natural history of this condition is still unknown.⁷⁴ Initially, the seizure type is usually simple partial; however, some patients have complex partial seizures,⁷⁵ and the seizures



Fig. 49.5 An infant with a port-wine stain in a bilateral cranial nerve V₁ distribution. Bilaterality is uncommon but can be present in up to 10% of patients.

may cluster, alternating with periods of seizure freedom.^{10,75,76} Rarely, patients with SWS can have infantile spasms.^{77,78} In patients with isolated leptomeningeal involvement (type 3), the seizures usually begin later and are more easily controlled with AEDs.⁶³

“Strokelike episodes” can occur, with prolonged hemiparesis persisting days to months or even permanently; these episodes are of longer duration than the usual Todd paralysis.⁷⁵ Seizures, minor traumas, and migraine headaches have been reported as precipitating events.^{75,79,80} Progressively, patients can develop spastic hemiparesis and visual field deficits, but the frequency of these developments has not been reported.⁷⁵

Headaches are a common complaint in patients who have SWS, with a frequency much higher than that in the general population.^{81,82} Migraines can be temporally related to seizures and strokelike episodes.⁸⁰

Cognitively and psychologically, patients range from normal to severely disabled. More severe cognitive deficits have been associated with the early onset of seizures, intractable epilepsy, multiple seizure types, a greater degree of cerebral atrophy, and bilateral involvement.^{69,73,75} School-age children are more likely to be diagnosed with attention deficit disorders.

Glaucoma develops in 30 to 70% of patients. Of those in whom glaucoma develops, 60% present in infancy and 40% in childhood or early adulthood.⁷³ Glaucoma is the result of ocular capillary venous vascular malformations.⁶⁸

49.2.4 Pathology and Genetics

Although there is no genetic inheritance of SWS, somatic mosaicism may play a role.⁷⁵ Embryologically, the constellation of findings associated with SWS point to the sixth week of fetal development for the timing of the dysfunction. In normal development, a vascular plexus forms around the cephalic portion of

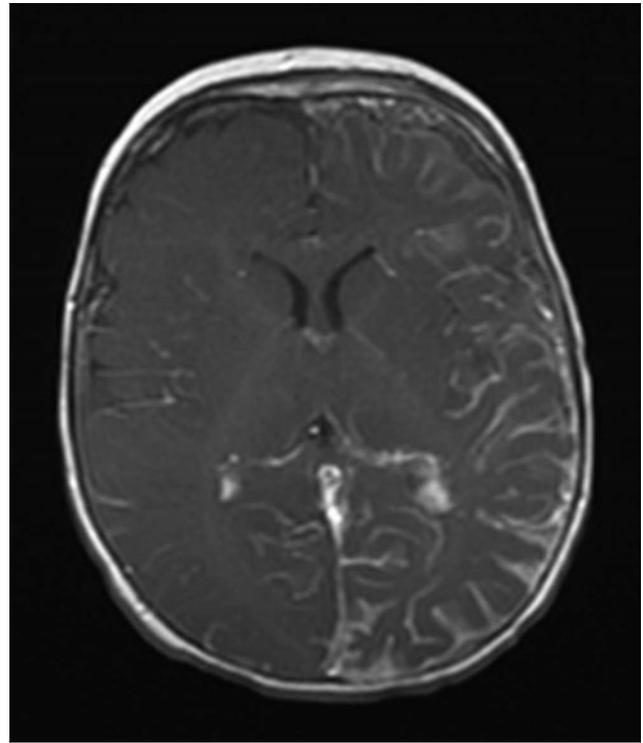


Fig. 49.6 Magnetic resonance (MR) imaging of the brain of an 11-month-old boy born with a left-sided port-wine stain in the distribution of cranial nerve V₁. Initial MR imaging at 7 months was normal. On this axial T1-with-contrast sequence, left hemispheric leptomeningeal angiomatosis is demonstrated.

the neural tube and in proximity to the ectoderm that will form the facial skin. Normally, this vascular plexus regresses during the ninth week of development. It is hypothesized that the vascular plexus fails to regress in SWS.^{65,83} Fibronectin expression may play a role in this process.^{3,84}

Pathologically, the normal vascular network of the brain is altered in SWS such that the cortical vessels are hypoplastic, the deep venous structures are usually dilated, and the leptomeningeal vessels are enlarged.⁵⁹ Microscopic examination reveals calcium in the cortex with gliosis and hypoplastic vessels.⁶⁵ Serial SPECT examinations demonstrate that blood supply to the affected cortex decreases progressively over the first year of life.⁸⁵ Also, during seizures, blood flow is significantly decreased in the surrounding brain, creating a vascular steal phenomenon.^{68,86} Therefore, seizures may exacerbate ischemia.⁸⁷

49.2.5 Diagnostic Studies

MR imaging is the radiologic test of choice for diagnosing leptomeningeal angiomatosis, which is visualized best on T1-weighted contrasted images (► Fig. 49.6). A choroid angioma with hypertrophy or dilation of the ipsilateral choroid plexus can be noted in older children. Newer MR imaging sequences, such as susceptibility-weighted imaging, are improving the diagnostic sensitivity of MR imaging by detecting the cortical calcification and dilated transmedullary and subependymal veins that may precede other MR imaging findings.^{88,89}

Additionally, MR imaging perfusion and diffusion abnormalities have correlated with clinical findings such as hemiparesis, seizures, and cognitive performance.^{90–92} Computed tomography (CT) is also useful for demonstrating gyriform cortical and choroidal calcifications, which are often absent in infancy. Because of the vascular steal phenomenon, the affected part of the brain atrophies and the calvaria secondarily thickens.^{93,94}

When patients present with strokelike episodes, they typically undergo CT (to rule out hemorrhage), EEG, and MR imaging. MR imaging may reveal diffusion abnormalities that are not in a large-vessel distribution. These are believed to be due to microvascular stasis.^{75,95}

In an infant with a PWS, leptomeningeal angiomatosis can be difficult to diagnose because neither CT nor MR imaging is sensitive in this age group.⁸⁸ Imaging may need to be repeated between the ages of 1 and 2 years to rule out intracranial involvement. Generally, it can be assumed that if a child older than 1 year with a PWS is developing normally, without seizures, and has normal findings on neurologic examination and contrasted brain MR imaging, then leptomeningeal involvement is unlikely.^{59,88}

Metabolic neuroimaging modalities, such as fluorodeoxyglucose F 18 PET, can assist in a comparison of glucose utilization in the affected and unaffected hemispheres and potentially in making decisions about the timing and technique of epilepsy surgery.^{75,96,97}

49.2.6 Treatment

A multidisciplinary approach is required for the care of SWS patients. They often require the care of a neurologist, ophthalmologist, dermatologist, and potentially a neurosurgeon. Because of the risk for glaucoma, even in infants, an ophthalmologist should be involved in the care of children with SWS.⁷⁵ Neurologists can treat migraines with the same strategies that are used for patients without SWS.^{75,98}

Neurologists can medically control seizures in 40% of cases.⁷⁰ When medical control cannot be obtained, surgery is considered. Because the neurocognitive and neurologic deficits can be progressive, determining the timing of surgery can be difficult. Surgeons differ on the optimal timing of the surgery. To prevent the adverse effects of continued seizures, some surgeons advocate early surgery.^{70,74,99} Others think it is better to be more selective because of the potential for gaining seizure control with AEDs and the possible complications of surgery.¹⁰⁰

Multiple surgical techniques have been employed, but hemispherectomy is the most effective in obtaining long-term control, and surgeons have reported good functional and quality-of-life outcomes.^{70,101} Hemispherectomy was first performed for this condition by Falconer and Rushworth.⁶² It is not clear whether there is an advantage of functional versus anatomical hemispherectomy in this patient population. Hemispherectomy is a reasonable choice for children with intractable epilepsy, hemiparesis, and visual field deficit. The more difficult decision pertains to the child with intractable epilepsy but without significant hemiparesis or visual field deficit.⁷⁵ Special considerations must be weighed regarding the child's vision. If a patient has normal visual fields, then the postoperative visual field deficit from a hemispherectomy

with the possibility of visual loss from glaucoma must be considered.⁵⁹ Although not as successful, more limited resections should be considered in patients without significant deficits. Surgery can be considered for patients with bilateral disease if monitoring localizes the seizures predominantly to one hemisphere.¹⁰²

The strokelike episodes are difficult to treat because their etiology is not completely understood, and the potential benefit of treating is debatable.⁷⁵ Because of the proposed etiology of microvascular stasis for this phenomenon, low-dose aspirin has been used with reports of decreased strokelike episodes and decreased seizures.^{103,104}

49.2.7 Prognosis

The prognosis depends on the severity of disease. There are no reasonable long-term studies reporting the lifetime prognosis for SWS patients. Neurocognitive and functional outcomes are the result of multiple factors, including seizures, AEDs, the vascular steal phenomenon, and cortical atrophy. Generally, patients who have better seizure control, either with AEDs or through surgery, have better outcomes.^{59,91}

49.3 von Hippel-Lindau Disease

49.3.1 Introduction

von Hippel-Lindau disease (VHL) is an autosomal-dominant genetic disorder that causes multiple neoplasms, including central nervous system (CNS) and retinal hemangioblastomas, pheochromocytomas, clear cell renal carcinoma, endolymphatic sac tumors, and pancreatic islet cell tumors. Renal and pancreatic cysts as well as epididymal and broad ligament cystadenomas can form.^{105,106}

In 1904, Eugene von Hippel, an ophthalmologist, described familial retinal angiomas,¹⁰⁷ later found to be histologically hemangioblastomas.¹⁰⁸ In 1926, Arvid Lindau, a pathologist, noted the association of these retinal hemangioblastomas and cerebellar hemangioblastomas.¹⁰⁹ There are now diagnostic criteria based on family history and clinical findings.¹⁰⁷

Although VHL-associated neoplasms develop relatively early compared with their sporadic counterparts, VHL remains primarily an adult disease.¹¹⁰ However, children can present with VHL.^{111,112}

49.3.2 Epidemiology

The incidence of VHL is 1 in 30,000 to 1 in 50,000 live births.^{113,114} It affects both sexes equally and can be found in all ethnic groups. There is a 90% penetrance by the age of 65.¹¹⁵ VHL accounts for a third of all CNS hemangioblastomas, more than half of retinal hemangioblastomas, and 1% of RCCs in the general population.¹¹⁶

49.3.3 Clinical Presentation

CNS hemangioblastoma is responsible for the presenting symptoms of 40% of patients at the time of VHL diagnosis.¹⁰⁵ These vascular tumors ultimately manifest in 60 to 80% of patients with VHL.^{105,117} Overall, VHL causes 5 to 30% of all cranial

hemangioblastomas and 80% of all spinal hemangioblastomas.¹¹⁸ The average age at a diagnosis of CNS hemangioblastoma is 29 years, although childhood cases are by no means rare.¹¹⁰ These tumors are most commonly located in the posterior fossa (75%), predominantly in the cerebellum but occasionally in the brainstem, and in the spinal cord (25%).^{119,120} The presenting symptoms are related to local mass effect, which can differ depending on whether the tumor is in the cerebellum, brainstem, or spinal cord. Because of this mass effect, posterior fossa hemangioblastomas often cause hydrocephalus. Additionally, the hemangioblastomas cause polycythemia in 5 to 20% of patients.¹¹⁸ Rarely, CNS hemangioblastomas are located in the supratentorial compartment.¹²¹

Retinal hemangioblastomas are the most common finding at presentation, and in half of cases, lesions are multiple or bilateral.¹²² By 50 years of age, the incidence of loss of vision is 35% in all *VHL* gene carriers and 55% in patients diagnosed with a retinal hemangioblastoma. Only 5% of cases are diagnosed before the age of 10 years.¹²³

Pheochromocytomas are important for neurosurgeons to identify because of their potential effect on operative conditions and postoperative care.¹²⁴ The incidence varies depending on the type of *VHL* (discussed below), but in most types the incidence ranges from 8 to 17%.¹⁰⁸ Pheochromocytomas can cause palpitations, unstable blood pressure, sweating, and headaches. Unlike most other *VHL* neoplasms, they are more likely to be detected in children and young adults than in older patients.¹²⁵

Endolymphatic sac tumors are present in 11% of patients and are usually asymptomatic at the time of diagnosis. When they do cause symptoms, hearing loss is usually the chief complaint, but they can also cause tinnitus and vertigo. With a mean age at diagnosis of 22 years, they can affect children.¹²⁶

The kidneys are affected with both clear cell renal carcinoma and renal cysts, but neither usually causes the initial presenting symptoms of *VHL*.^{118,127} Although the incidence of RCC varies depending on the type of *VHL*, in the most common types, the lifetime risk is about 70%.¹¹⁰ *VHL* is the most common cause of hereditary kidney cancer.¹⁰⁸ The average age at presentation is 40 years¹²⁸ however, asymptomatic lesions are frequently diagnosed earlier, but rarely before the age of 16 years.¹²⁹

Islet cell tumors and cysts affect the pancreas. Usually, the islet cell tumors are nonsecreting, and the cysts do not normally affect function.¹³⁰

49.3.4 Pathology and Genetics

Inheritance is autosomal-dominant, with about 20% of cases sporadic.¹¹⁸ The *VHL* tumor suppressor gene was mapped to chromosome 3p25.¹³¹ Many gene mutations have been discovered, creating a complicated genotype–phenotype relationship.¹³² Certain genotypes are more likely to be associated with specific tumors, such as pheochromocytomas, which has led to the definition of different “types” of *VHL*.^{116,133} The mutations can be missense, nonsense, or deletions.^{134,135} Prenatal testing is available.¹³⁶

Histologically, CNS and retinal hemangioblastomas are identical. These tumors are benign and highly vascular, consisting of large, lipid-laden stromal cells supported by a well-developed capillary network with many mast cells. The stromal cells show hyperchromasia and atypia, but almost no mitoses. The cyst fluid has a high concentration of erythropoietin.^{108,137}

49.3.5 Diagnostic Studies

In 1964, clinical diagnostic criteria were first proposed by Melmon and Rosen after review of the literature.¹⁰⁷ In a patient with a positive family history, the diagnosis is made if a single *VHL*-associated tumor is discovered. In the 20% of patients with sporadic *VHL*, either two or more CNS or retinal hemangioblastomas or a single hemangioblastoma and one other *VHL*-associated neoplasm must be present.^{107,134}

On CT and MR imaging, CNS hemangioblastomas have characteristic findings, which include a cystic component and an enhancing mural nodule (► Fig. 49.7). Spinal cord hemangioblastomas have an enhancing intramedullary component, often with a cystic component and associated syrinx. CNS hemangioblastomas often have large feeding and draining vessels.¹³⁸ The differential diagnosis can include juvenile pilocytic astrocytoma, ependymoma, and arteriovenous malformation.^{118,120,139}

Endolymphatic sac tumors are best diagnosed on MR imaging of the brain with and without contrast to evaluate for an enhancing mass, and on thin-cut CT through the temporal bone to evaluate for bone erosion associated with these tumors. Sometimes, these tumors can be occult on imaging.^{140,141}

CT and MR imaging of the abdomen can assist with the diagnosis of pheochromocytoma; however, laboratory tests are the gold standard. The diagnosis can be made with the measurement of either plasma fractionated metanephrines in high-risk patients or 24-hour urine fractionated or total metanephrines and catecholamines in lower-risk patients.¹⁴²

Screening recommendations have been proposed by Maher et al.¹¹⁶ Patients with *VHL* should undergo screening MR imaging of the brain and possibly spine every 1 to 3 years beginning

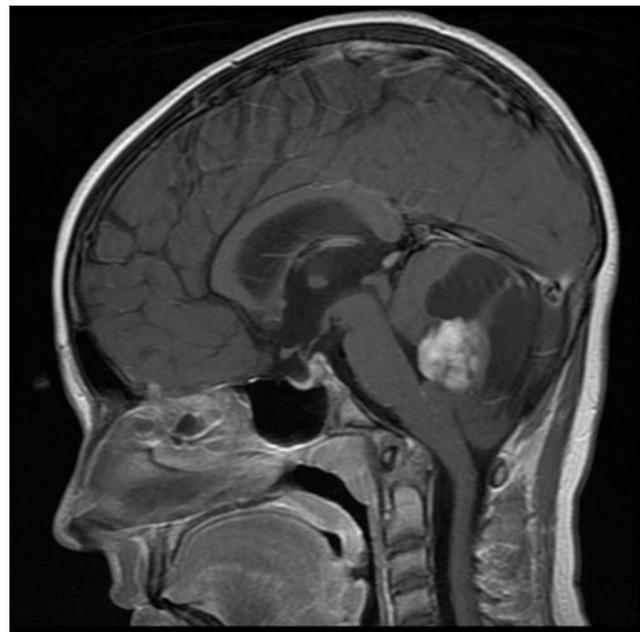


Fig. 49.7 Magnetic resonance imaging of the brain of a 10-year-old with von Hippel-Lindau disease. On this sagittal T1-with-contrast sequence, a posterior fossa hemangioblastoma is present, with the characteristic cystic component and enhancing mural nodule.

in adolescence. An ophthalmologist should screen for retinal hemangioblastomas annually beginning in infancy or childhood. Annual renal and pancreatic screening MR imaging or ultrasound should begin at the age of 16 years. For pheochromocytoma, blood pressure monitoring and 24-hour urine catecholamine metabolite studies should be performed annually beginning in childhood. In families at higher risk for pheochromocytoma, more intense surveillance, including annual plasma normetanephrine level measurement and adrenal imaging beginning at the age of 8 years, should be considered.

49.3.6 Treatment

Natural history studies of CNS hemangioblastomas describe saltatory growth patterns with intermittent, unpredictable periods of quiescence and growth.^{112,117,143} Not all tumors cause symptoms. In VHL, it is recommended that tumors be treated only when they are causing symptoms.^{112,141,143,144} Symptomatic tumors almost universally are associated with either cysts or peritumoral edema.¹⁴⁴ At this time, there is no way to predict which tumors will progress to cause symptoms and require surgical treatment.

Angiography can be useful for defining the vascular anatomy. Preoperative embolization has been used; however, it is often not possible because much of the blood supply may be provided by multiple small vessels that cannot be embolized.¹⁴¹ Also, there have been reports of significant morbidity and mortality associated with embolization of these tumors.^{145,146}

Surgical resection of symptomatic CNS hemangioblastomas is the recommended therapy. Because of the vascularity, careful microsurgical technique must be employed. Extracapsular dissection with careful coagulation and transection of tumor vessels is recommended.^{144,147,148} Disruption of the tumor capsule can cause troublesome bleeding. When there is an associated cyst, the cyst capsule is maintained as long as possible to assist with dissection. The cyst wall does not require resection because it is only compressed gliotic tissue.¹⁴⁹

A similar approach should be taken with spinal cord hemangioblastomas. In symptomatic lesions, surgical resection should be undertaken. Poor outcomes have been associated with a ventral location and not presenting to the pial surface.¹⁵⁰

Other treatment strategies include stereotactic radiation, with reports of short-term tumor control over 90%.¹⁵¹ However, at 15 years of follow-up, tumor control decreases to 51%.¹⁵²

In patients requiring surgical treatment of a CNS hemangioblastoma who also harbor a pheochromocytoma, alpha- and beta-adrenergic blockade must be employed preoperatively to safely manage the blood pressure perioperatively.¹⁵³

The treatment of other tumors associated with VHL is beyond the scope of this chapter.

49.3.7 Prognosis

The early diagnosis of retinal hemangioblastomas and RCCs has improved patient outcomes.¹¹⁰ The most common causes of death are RCC and complications of CNS hemangioblastomas. The median life expectancy is 49 years.^{118,154} Because of the availability of genetic testing and the potential for early diagnosis in familial cases, life expectancy may potentially be extended with early diagnosis and treatment.¹³⁶

49.4 Hereditary Hemorrhagic Telangiectasia

49.4.1 Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is one of the most prevalent autosomal-dominant conditions; there are only rare sporadic cases. The incidence is estimated to be 1 in 5,000 live births.¹⁵⁵ Genetic testing is available and is positive in 85% of cases.¹⁵⁶ The genetic mutations causing HHT have been linked to chromosomes 9q,¹⁵⁷ 12q,¹⁵⁸ 5q,¹⁵⁹ 18q, and 7p.¹⁶⁰

The syndrome is characterized by visible cutaneous telangiectases, mucosal telangiectases causing recurrent epistaxis and gastrointestinal bleeding, and the potential for multiple-organ arteriovenous malformations (AVMs).¹⁶¹ Telangiectases are usually located on the lips, tongue, face, fingers, and mucosa. They are pink to red pinhead-size lesions, or sometimes elevated, purple lesions. They can be differentiated from petechiae because they blanch with pressure and then immediately refill.¹⁶² The cutaneous stigmata of HHT are not present at birth but evolve and progress with age.¹⁶³ AVMs can form in the brain, spine, lungs, and liver. These patients also have higher incidences of anemia and thromboemboli due to elevated factor VIII levels, which occur in nearly 7% of patients.¹⁶⁴ The average age at the onset of epistaxis is 12 years.¹⁶³ Penetrance is age-related, approaching 100% by age 40.¹⁵⁵

The diagnosis is made with the Curaçao criteria, which include the presence of epistaxis, telangiectases, visceral lesions, and family history. Patients are given the diagnosis of unlikely, possible, or definite HHT depending on the number of clinical criteria that are met.¹⁶⁵ Genetic testing can be used to define the specific mutation in a family and then test other members of the family who may not meet the diagnostic criteria. Prenatal genetic testing can be performed for affected families. However, the benefit of such diagnosis has not been defined.¹⁶⁶

Although there is no definitive life expectancy study, a number of reports indicate that life expectancy is likely lower for all patients with HHT because of the risks for death early in life from cerebral AVMs^{167,168} and for pregnancy-related maternal deaths; there is a 1% risk for maternal or fetal death with pregnancy.¹⁶⁹ Five different types of HHT have been identified, and each is associated with different risk for certain AVMs.¹⁷⁰

49.4.2 Neurosurgical Implications

Up to 23% of patients with HHT also have some type of cerebral vascular malformation. Most commonly, these lesions are AVMs, arteriovenous fistulas, cavernous malformations, and telangiectases.¹⁷¹ Current HHT guidelines recommend that children and adults with possible or definite HHT (by the Curaçao criteria) be screened with MR imaging. Patients with an AVM diagnosed on MR imaging should be referred for more specific testing and treatment.¹⁶⁶ If a person's childhood screening MR imaging study is negative for a vascular malformation, there is insufficient evidence to recommend regular follow-up screening with MR imaging; however, consideration should be given to another single screening MR imaging study at the beginning of adulthood.¹⁶⁶ AVMs should be treated by neurosurgeons using the same clinical approach that they would use for sporadic

AVMs, including the possibilities of microsurgery, stereotactic radiation, and embolization.^{172–174}

Pulmonary AVMs occur in 15 to 50% of patients, and in addition to respiratory complications, there are multiple potential neurologic sequelae.^{175–177} Because of paradoxical embolism with right-to-left cardiovascular shunt, patients are at risk for transient ischemic attacks, ischemic strokes, and cerebral abscesses.¹⁷⁷ In fact, neurologic symptoms in HHT are more likely to be due to an ischemic stroke than to a hemorrhage from a cerebral AVM.^{167,177}

Fewer than 1% of patients develop spinal AVMs, which may present with paraparesis, paraplegia, myelopathy, or pain.^{18,19} No specific screening recommendations for spinal AVMs exist, but if an AVM is suspected, then MR imaging can be performed.¹⁶⁶ Treatment depends on the type of spinal AVM but can include embolization or microsurgery.¹⁷⁸

49.5 Basal Cell Nevus Syndrome

49.5.1 Introduction

Basal cell nevus syndrome (BCNS) is also known as Gorlin syndrome, Gorlin-Goltz syndrome, nevoid basal cell carcinoma, and basal cell carcinoma nevus syndrome. It has autosomal-dominant inheritance and is associated with the formation of basal cell carcinomas, odontogenic keratocysts, and skeletal anomalies. It was first defined as a syndrome in 1960 by Drs. Gorlin and Goltz.¹⁷⁹ The association between BCNS and medulloblastoma was first described by Herzberg and Wiskemann in 1963.¹⁸⁰ BCNS occurs in about 1 in 57,000 live births.¹⁸¹ The genetic mutations have been identified in the sonic hedgehog pathway.^{182,183} According to a consensus statement,¹⁸⁴ a diagnosis of BCNS can be reasonably considered if any of the following criteria are met: one major criterion and molecular confirmation, two major criteria, or one major and two minor criteria (see box “Diagnostic Criteria for Basal Cell Nevus Syndrome (p.650)”).

Diagnostic Criteria for Basal Cell Nevus Syndrome

- Major criteria
 - Basal cell carcinomas or number out of proportion to prior sun exposure and skin type before the age of 20 years
 - Odontogenic keratocyst of the jaw before the age of 20 years
 - Palmar or plantar pitting
 - Lamellar calcification of the falx cerebri
 - Medulloblastoma, typically desmoplastic
 - First-degree relative with basal cell nevus syndrome
- Minor criteria
 - Rib anomalies
 - Other skeletal malformations
 - Macrocephaly
 - Cleft lip/palate
 - Ovarian/cardiac fibroma
 - Lymphomesenteric cysts
 - Ocular abnormalities

Data from Bree AF, Shah MR. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am J Med Genet A* 2011;155A(9):2091–2097.¹⁸⁴

Genetic testing is not required for diagnosis, and its sensitivity can be low.^{184,185} However, it can be helpful in selected cases, such as patients undergoing prenatal screening and patients who do not meet the clinical diagnostic criteria. In these cases, genetic confirmation could guide future screening tests to improve outcomes or the management of affected family members who do not yet meet the clinical criteria.¹⁸⁴

It is recommended that children diagnosed with BCNS undergo yearly evaluations by a geneticist to ensure that all multidisciplinary needs are being addressed. These patients require serial examinations and tests for the early detection of associated tumors and conditions.¹⁸⁴

49.5.2 Neurosurgical Implications

It is recommended that children up to the age of 8 years undergo annual brain MR imaging with and without contrast to evaluate for medulloblastoma.¹⁸⁴ When associated with BCNS, medulloblastoma is usually diagnosed in the first 2 years of life.¹⁸⁶ Medulloblastomas occur in 5% of patients with BCNS¹⁸⁷ in a male-to-female ratio of 3:1.¹⁸⁸ Often, the medulloblastoma can be the initial finding of BCNS, so careful evaluation for other diagnostic criteria should ensue.¹⁸⁹ Histologically, the medulloblastomas that form are desmoplastic and genetically linked to a loss of heterozygosity on chromosome 9q.¹⁹⁰ The prognosis of treated medulloblastomas associated with BCNS is better than that for sporadic medulloblastomas.^{186,190,191} Treatment includes aggressive resection, chemotherapy, and sometimes radiotherapy, although the administration of radiotherapy is somewhat controversial because of the high risk for radiation-induced basal cell carcinoma in this syndrome as well as other radiation-related tumors, such as sarcomas.^{186,192–194}

For spinal evaluation, it is recommended that these children undergo a first X-ray evaluation for scoliosis at the age of 1 year. If the result is abnormal, then the evaluation should be repeated every 6 months. If the result is normal, then the evaluation should be repeated if the child becomes symptomatic.¹⁸⁴ Spina bifida occulta, bifid vertebrae, and fused vertebrae are all associated with this syndrome.^{189,195}

These patients can also have macrocephaly,^{189,196} with abnormal head shapes and hypertelorism.¹⁹⁷ In 50% of patients, the head circumference is above the 95th percentile.^{189,196}

49.6 Neurocutaneous Melanosis

49.6.1 Introduction

First described in 1861 by von Rokitansky¹⁹⁸ and named in 1948 by Van Bogaert,¹⁹⁹ neurocutaneous melanosis (NCM) is a rare, sporadic, nonheritable disorder characterized by large congenital cutaneous melanocytic nevi and benign or malignant leptomeningeal melanosis. Hypothetically, it develops from a disorder in embryonic neuroectodermal morphogenesis resulting in the abnormal proliferation of melanin-producing cells.^{200–202}

NCM is equally prevalent in men and women,²⁰³ and the age at presentation is bimodal. Most frequently, NCM presents in the first 2 years of life²⁰¹; however, in a minority of patients, it presents the second and third decades of life.^{203,204} NCM can be



Fig. 49.8 A 2.5-year-old boy exhibiting multiple melanotic nevi associated with neurocutaneous melanosis.



Fig. 49.9 Magnetic resonance imaging of the cervical spine of an 18-month-old boy with neurocutaneous melanosis. On this sagittal T1-with-contrast sequence, leptomenigeal enhancement is demonstrated.

associated with other neurocutaneous disorders, such as neurofibromatosis type 1 and Sturge-Weber syndrome.²⁰⁵

Children with large cutaneous melanocytic nevi have a 1 to 12% chance of developing NCM.^{206–208} In two-thirds of patients, there is a giant nevus, usually located over the lumbosacral spine; in the remaining one-third, there are multiple smaller nevi (► Fig. 49.8).^{203,204} Malignant degeneration of leptomenigeal melanosis occurs in 40 to 60% of cases, leading to leptomenigeal melanoma.²⁰¹ Additionally, malignant transformation of the skin lesions can occur in 5 to 15% of patients; therefore, some dermatologists recommend prophylactic resection of some of these lesions.^{209,210}

The diagnostic criteria include the following: the presence of large or multiple congenital nevi (>20 cm in adults, ≥9 cm on the head or ≥6 cm on the body in infants); no evidence of cutaneous malignant change, except in patients with benign meningeal lesions; and no evidence of meningeal melanoma, except in patients with histologically benign skin lesions.²⁰¹

Definitive diagnosis requires histologic confirmation, which is often made only at autopsy; otherwise, the diagnosis remains provisional.^{200,201} Cerebrospinal fluid (CSF) sensitivity is only about 40%.^{201,211} Fortunately, MR imaging of the brain and spine is sensitive for detecting melanin in the leptomeninges.²¹² MR imaging is the diagnostic evaluation of choice for NCM. On MR images, the leptomenigeal melanosis appears hyperintense on T1 sequences and hypointense on T2 sequences because of the paramagnetic properties of melanin.^{213–215} Upon contrast administration, diffuse leptomenigeal enhancement of the brain and spine is often described (► Fig. 49.9).^{215,216}

49.6.2 Neurosurgical Implications

Hydrocephalus develops in about 60% of cases and often causes the presenting symptoms of the leptomenigeal process.^{209,217,}

²¹⁸ In NCM, hydrocephalus develops through multiple mechanisms: leptomenigeal infiltration by melanin causing direct obstruction to flow, decreased CSF resorption at the site of the arachnoid villi, or a Dandy-Walker complex.^{209,219} About 10% of patients with NCM have a Dandy-Walker complex.²²⁰ The developmental mechanism of the Dandy-Walker complex is hypothesized to be melanocyte infiltration of the cerebellum causing abnormal development and fourth ventricular outlet obstruction.^{201,221} The melanocytes can also invade the parenchyma, commonly the anterior temporal lobe and amygdala, causing seizures.²⁰⁵ NCM can cause many symptoms and signs²¹⁹ developmental delay²²² epilepsy, which can be intractable²²³ quadra- or paraplegia^{213,222} chronic psychosis²²⁴ and movement disorders.²²⁵ The spine is involved in about 20% of cases.²⁰⁵

Treatment includes ventriculoperitoneal shunting for the alleviation of hydrocephalus. Because there is rarely a focal lesion, such as a CNS melanoma, to be removed, resective surgery is generally not an option. Radiation and chemotherapy have not been found to be effective.^{226–228}

The prognosis is poor. Once they become symptomatic from the leptomenigeal process, half of patients die within 3 years,²⁰¹ and this appears to be independent of whether histologically they have a melanoma or benign melanosis.^{219,} ²²⁷ Patients with an associated Dandy-Walker complex have a poorer prognosis, usually dying before the age of 4 years.²²¹

Pearls

1. The management of each syndrome requires a multidisciplinary approach, and after diagnosis, many patients require regular surveillance screening tests.
2. Genetic testing is available for most of these conditions. However, diagnoses are made with criteria that do not include the results of genetic testing.
3. In TSC, the mTOR pathway inhibitors are promising treatments, with the potential to change treatment paradigms in SEGAs and epilepsy.
4. Patients with TSC and SWS are often candidates for epilepsy surgery.
5. Patients with TSC, VHL, or BCNS often develop CNS tumors requiring neurosurgical intervention.

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50 Chemotherapy and Biologic Therapy for Pediatric Brain Tumors

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The current management of primary central nervous system (CNS) tumors of childhood has resulted in slowly improving survival rates and has become increasingly complex. Until the late 1970s and early 1980s, treatment for children with both benign and malignant brain tumors primarily consisted of surgery with or without radiation therapy. Chemotherapy was restricted to children with recurrent malignant brain tumors, usually with the goal of transiently prolonging life. A series of clinical investigations completed over the past quarter century has demonstrated the efficacy of chemotherapy for children with recurrent and newly diagnosed malignant and benign primary CNS tumors. For some brain tumors, such as medulloblastomas and possibly high-grade gliomas, chemotherapy at the time of diagnosis, when added to radiation therapy, improves the likelihood of survival.¹⁻³ Furthermore, for some children with nondisseminated disease, chemotherapy may allow a reduction in the dose of radiotherapy needed.⁴ In infants and very young children, chemotherapy is being increasingly used to delay, if not obviate, the need for alternative treatments.⁵ To date, the chemotherapies used to treat brain tumors have been primarily conventional cytotoxic agents, which relatively nonselectively kill tumor cells. However, recently, a host of biological agents have become available that are designed to target tumor cells and are in clinical trials.^{6,7} The specific role of this or any other type of chemotherapy in the management of childhood brain tumors is still being defined.

50.1 General Considerations

Discussions of the role of chemotherapy for childhood brain tumors have to take into account many factors. Childhood primary tumors of the CNS comprise a heterogeneous group of lesions. Generalizations are difficult to make, given the histologic and biological heterogeneity of these lesions.^{8,9} Even within recognized groupings—for example, medulloblastomas—there are now well-accepted molecular subgroupings, with likely different sensitivities to treatment and different prognoses.¹⁰ Obviously, for a chemotherapeutic agent to be effective, the tumor must be sensitive to the agent employed. The selection of a drug or drug regimen that is most likely to be effective for a given type of tumor has been primarily based on clinical studies investigating the response of the tumor to treatment.¹¹ Laboratory methods have been established to facilitate analysis of the biology and the therapeutic profile of a given tumor. Such laboratory approaches result in a more rational choice of chemotherapeutic agents to be evaluated. Agents with possible activity are tested by *in vitro* methods, and selected agents are further studied in animal models, such as a xenograft model in which human tumors are grown in immunodeficient (nude) mice. This rigorous means of testing allows potentially active new compounds to be identified before clinical trials are

undertaken. For biological agents, which may affect not only specific targets, such preclinical testing is likely even more important. Yet other factors, such as the ability of an agent to reach a tumor in effective concentrations, remain crucial.

50.2 Types of Drug Trials

The majority of drugs presently in use were chosen on the basis of their efficacy against other forms of cancer and subsequent results in clinical trials in adults and children with brain tumors (► Table 50.1). In general, these clinical trials can be separated into three major categories (► Table 50.2). Phase I trials are the initial trials, and the purpose of such studies is to determine the maximum tolerated dose of the drug, to identify its toxicities, and often to perform detailed pharmacokinetic studies. These studies are carried out in children with recurrent disease in whom all proven means of therapy have been exhausted. In pediatrics, the majority of drugs used for patients with brain tumors in Phase I testing have already been demonstrated to be somewhat efficacious in adults with primary CNS tumors. Many of the active antitumor agents now in use for patients with newly diagnosed brain tumors initially were tested in these Phase I clinical trial settings.

Once the optimal dose and schedule of a drug have been defined in a Phase I study, a Phase II trial is undertaken to determine the response rate of a specific tumor to the drug. The predominant measure of the efficacy of a drug in such trials is the objective response of the tumor to treatment, with a more than 50% reduction in tumor size on neuroradiographic studies considered a partial response and a complete disappearance of tumor considered a complete response. However, time to progression may also be used as a measure of effectiveness. Phase II trials are predominantly undertaken in children with recurrent disease. However, for some tumor types, especially those that are highly resistant to any known form of treatment, preradiation chemotherapeutic Phase II trials (which have also been titled *neoadjuvant trials*) have been performed. Reasons for using preradiation chemotherapeutic trials include that patients may be better able to tolerate a drug or drugs before other forms of therapy (primarily radiation therapy) have been delivered and that prior therapy may make a tumor more resistant to the effects of chemotherapy, thus causing active agents to be incorrectly considered ineffective.

The final step in the evaluation of the efficacy of a chemotherapeutic agent or a group of drugs is a randomized comparison of the efficacy of the drug or regimen, either in addition to conventional therapy or instead of conventional therapy, versus that of standard therapy. Given the relative rarity of pediatric CNS tumors, Phase III studies usually must be undertaken in a multi-institutional setting.

Table 50.1 Most common chemotherapeutic agents used for childhood brain tumors

Drug	Route	Tumor type	More common toxicities
Alkylating agents			
Cyclophosphamide	IV	Medulloblastoma Germ cell tumors	Myelosuppression Hemorrhagic cystitis
Ifosfamide	IV	Medulloblastoma	Hemorrhagic cystitis Reproductive
Melphalan	IV (ABMR)	? Medulloblastoma ? High-grade glioma	Myelosuppression Gastrointestinal
Thiotepa	IV (ABMR)	? Medulloblastoma ? High-grade glioma	Myelosuppression
CCNU (BCNU)	PO (IV)	Medulloblastoma High-grade glioma Oligodendroglioma	Myelosuppression Gastrointestinal Pulmonary
Cisplatin	IV	Medulloblastoma ? Ependymoma Germ cell tumors	Ototoxicity Nephrotoxicity Myelosuppression Peripheral neuropathy Nausea and vomiting
Carboplatin	IV	Low-grade glioma Medulloblastoma ? Ependymoma Germ cell tumors	Peripheral neuropathy Nausea and vomiting Myelosuppression
Procarbazine	PO	? High-grade glioma ? Low-grade glioma ? Oligodendroglioma	Myelosuppression Nausea and vomiting
Temozolomide	PO	? High-grade glioma ? Low-grade glioma ? Other	Myelosuppression Hepatotoxicity
Antimetabolites			
Methotrexate	PO, IV, ? IT	? Medulloblastoma ? High-grade glioma	Myelosuppression Gastrointestinal Hepatotoxicity
Cytosine arabinoside	IV, ? IT (? ABMR)	? Medulloblastoma	Gastrointestinal Hepatic
Plant alkaloids			
Vincristine	IV	Medulloblastoma Low-grade glioma ? High-grade glioma	Peripheral and autonomic neuropathy
Etoposide (VP-16)	IV or PO	? Medulloblastoma ? High-grade glioma ? Low-grade glioma Germ cell tumors	Myelosuppression

Abbreviations: ABMR, autologous bone marrow rescue; BCNU, bischloroethyl-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; IT, intrathecal; IV, intravenous; PO, orally.

50.3 Determinants of Drug Efficacy and Drug Resistance

The efficacy of a chemotherapeutic agent is not dependent solely on the sensitivity of a tumor to the drug. Other factors are also of importance, including the following: pharmacokinetics of the drug, host pharmacogenomics, concurrent use of medications that may alter drug metabolism through the cytochrome P-450

system of the liver, ability of the chemotherapeutic agent to reach the tumor site in high enough concentrations to affect tumor growth, ability of the tumor cells to accumulate and retain the drug, and ability of the tumor cells to repair drug-induced damage.^{12–14} A great deal of emphasis has been placed on the delivery of the drug, or drugs, to the tumor, but increasing information suggests that equally important factors may be the cellular mechanisms within the tumor responsible for drug resistance.

Table 50.2 Investigational trials

Type	Goal	Patient population
Phase I	Determine maximum tolerated dose; ? dose searching	Recurrent tumors without known effective treatments; 15 to 30 patients
Phase II	Determine spectrum of agent; estimate disease-specific response rate	Recurrent tumors; newly diagnosed refractory tumors; 15 to 30 patients per tumor type
Phase III	Determine if more effective than currently available therapy	Usually newly diagnosed; often randomized

The blood–brain barrier has been identified as a major reason for the ineffectiveness of certain chemotherapeutic agents.^{15–17} In some pediatric brain tumors, such as medulloblastomas, which often have an abundant blood supply, the significance of the blood–brain barrier is unclear. For infiltrating gliomas, it is well documented that drug delivery is a more important issue because it is often difficult to deliver adequate concentrations of drugs to the periphery of the tumor.^{15–17} A variety of means have been used in attempts to improve drug delivery, including higher doses of chemotherapeutic agents, osmotic agents to disrupt the barrier, and more recently chemotherapeutic agents coupled with other drugs that selectively disrupt the tumor blood–brain barrier.^{15–19} For example, the anti-angiogenesis drug cilengitide, which targets integrins on ne endothelium, was found to improve the outcome of adult patients with glioblastoma multiforme (GBM) when it was administered with temozolomide chemotherapy; however, improvement was demonstrated only in those patients with tumors exhibiting MGMT (O6-methylguanine DNA-methyltransferase) promoter methylation, which confers sensitivity to temozolomide. This finding suggests that in this setting cilengitide was helping to increase the effective concentration of temozolomide delivered to temozolomide-sensitive tumors through its effect on normalization of the tumor vasculature.²⁰

The goal of high-dose chemotherapy is to increase the delivery of cytotoxic agents to tumor effectively by overcoming the limited permeability of the blood–brain barrier. Predominantly lipid-soluble alkylating agents with nonoverlapping hematologic toxicities have been chosen. Initially, trials were performed with one cycle of chemotherapy supported by autologous bone marrow transplant, but this type of support has been primarily supplanted by peripheral blood stem cell support. Toxicity with autologous bone marrow transplant protocols has been significant; in early trials, it was associated with a 5 to 15% treatment-related mortality rate.^{21–23} In recent investigations, the administration of less intensive drug regimens multiple times with peripheral blood stem cell support has resulted in decreased morbidity and mortality.²⁴

Other methods, such as intra-arterial therapy, intracavitary therapy, the use of biodegradable polymers intraoperatively impregnated with a chemotherapeutic agent (allowing a slow local release of the agent–wafer therapy), and direct intraparenchymal infusional therapy, are also being used in attempts to increase delivery to the local tumor site.^{25–31} Most recently, the use of circulating nanoparticles conjugated to tumor-targeting molecules and radioisotopes, chemotherapeutic agents, or other biological agents has been explored experimentally with some success.^{32,33} The first human adult cancer trials using therapeutic nanoparticles started in 2012.

Direct delivery to tumors via the infusion of toxins conjugated to agents that selectively bind tumor cells is under study in both adults and children with brain tumors. Such approaches, which use convection delivery techniques, are appealing yet potentially extremely toxic. Convection delivery has been shown to deliver agents quite extensively throughout the brain, but it is unclear whether the conjugated toxin is best delivered into the tumor or in the area around the tumor. The selectivity of tissue damage is also unclear. Although these are potentially useful techniques, their efficacy has not yet been clearly shown in either adults or children with brain tumors.

The mechanisms of drug resistance in primary CNS tumors are actively being defined.³⁴ Resistance to a given therapy may be an intrinsic property of a tumor or may be acquired after treatment. Tumors may acquire resistance by the loss of normal properties or by the amplification of existing mechanisms in the cells. Tumors may become cross-resistant to a whole group of drugs by a similar mechanism. Mechanisms of drug resistance include alterations in cell transport, the expression or amplification of genes like the multidrug resistance gene, and elevated intracellular levels of enzymes that interfere with the antitumor activity of a drug. The efficacy of the alkylator agents, at present one of the most widely used classes of drugs for the treatment of CNS tumors, is decreased by elevated levels of intracellular aldehyde dehydrogenase and glutathione or glutathione *S*-transferase.^{35–38} Similarly, intrinsic or acquired resistance to the nitrosoureas may be due to increased repair of DNA mediated by the O6-alkyl guanine DNA alkyl transferase protein or by elevated levels of thiol or glutathione *S*-transferases.^{35–38} A variety of techniques have been used in an attempt to overcome mechanisms of drug resistance, such as saturation of enzymes by alternative substrates or inactivation of cell resistance mechanisms by drugs, but none have shown a clear improvement in efficacy. One such approach under active study is the drug O6-benzylguanine, which depletes alkyl glutathione *S*-transferase levels. This enzyme-depleting drug was initially given with bischloroethyl-nitrosourea (BCNU) but is now also under study to increase sensitivity to temozolomide, as well as to improve the efficacy of alkylator-impregnated polymer wafers placed, after tumor resection, into the rim of the resection cavity.

In 1979, Goldie and Coldman proposed a mathematical model that related curability of a malignancy to the appearance of resistant cell lines.^{39,40} They proposed that control of a neoplasm was a function of various factors favoring resistance, including the tumor's spontaneous mutation rate. An outgrowth of this theory is the concept that a tumor is less likely to be resistant to multiple agents administered simultaneously than it is to be resistant to individual agents because cells are not given an opportunity to mutate and develop pleiotropic multiple-drug resistance. Additionally, if drugs are given over a relatively

short time, myelosuppression should be less because damage to hematopoietic precursor cells depends partially on the duration of exposure. This concept has been widely tested in pediatric brain tumor trials. The majority of ongoing chemotherapeutic studies are using a combination of drugs rather than single agents in attempts to improve efficacy.

In pediatrics, the applications of chemotherapy have not been limited to the development of means to improve survival. Given the well-documented toxicities of radiation, especially whole-brain irradiation, chemotherapy has also been employed in attempts to reduce the amount of radiotherapy required for disease control and in some cases to delay, if not obviate, the need for radiotherapy.^{4,5} Chemotherapy is now widely used for infants and young children with malignant brain tumors and for selected patients with low-grade tumors that are not surgically resectable without prohibitive morbidity.

50.4 Biological Therapy

Conventional chemotherapy has consisted predominantly of drugs that cause cytotoxic damage, with considerable systemic and, at times, CNS toxicity. In theory, the use of biological therapy, which in principle selectively targets specific molecular aspects of the tumor, results in a better therapeutic window and the ability to deliver therapy with less toxicity and greater efficacy. This concept of sparing normal cells by using molecularly based therapy is intriguing and in many ways is the “Holy Grail” of future cancer treatment. However, currently available biological agents may be less specific in the targets they hit than originally thought, and the molecular mechanisms disrupted may also be critical for normal cellular function in the brain or other organs. Concepts of cellular signaling, signal transduction pathways involved in cell regulation, proliferation, and survival are rapidly evolving.^{41–43} The role of proto-oncogenes and tumor suppressor genes in some brain tumors is just beginning to be characterized. Other factors involved in cancer development and growth, such as neoplastic angiogenesis and tumor invasion and migration, are also likely crucial in sustaining tumor growth and facilitating tumor spread. Agents have recently been developed that target critical mechanisms for tumor growth and are quickly entering the therapeutic arena. However, to date, none of them have demonstrated clear efficacy in regard to long-term control of pediatric brain tumors, and their short- and long-term toxicities are still being elucidated. At the same time, because of the unique mechanisms of action and promise of these agents, there is tremendous interest in integrating them, as rapidly as possible, into the standard treatment of childhood brain tumors.

Receptor tyrosine kinases are transmembrane receptor proteins that regulate many critical cellular processes, including proliferation and cell survival.^{43–45} A host of tyrosine protein kinase inhibitors have been developed in attempts to arrest growth signaling. In tumors, signaling may be activated by a variety of different mechanisms, including overexpression of the tyrosine kinase and gain of function; at times, the receptor is constitutively activated (especially in adult cases of GBM) even without the presence of a ligand.⁴⁵ A variety of receptor tyrosine kinases have been implicated in brain tumor pathogenesis and thus are potential targets for therapy. These include

platelet-derived growth factor, epidermal growth factor, vascular endothelial growth factor, insulin-like growth factor, and fibroblast growth factor.^{6,46} The biological agents that have been used include small-molecule inhibitors, which target the intercellular tyrosine kinase domains, and monoclonal antibodies, which act predominantly against growth factor ligands.

Platelet-derived growth factor receptor, which predominantly comprises two receptors (alpha and beta), has been shown to mediate cell signaling pathways involved in tumor proliferation, survival, invasion, and angiogenesis. Amplifications of platelet-derived growth factor have been demonstrated in pediatric high-grade gliomas, diffuse intrinsic brainstem gliomas, and medulloblastomas.^{47,48} Imatinib, a small-molecule inhibitor of BCR/ABL kinase, KIT, and platelet-derived growth factor receptor, has been found to be useful in a variety of different tumor types; however, studies of brain tumors in children have found it to be relatively ineffective,^{49,50} possibly because of its poor CNS penetrance. Other platelet-derived growth factor receptor inhibitors are presently in clinical trials.

Epidermal growth factor receptor comprises four members and is expressed on actively dividing cells, not only in brain tumors but also in brain neurogenic niches, such as the subventricular zone.^{43,44,51–53} Overexpression and amplification of epidermal growth factor receptor have been reported in pediatric high-grade gliomas and brain stem gliomas, as well as ependymomas, medulloblastomas, and low-grade gliomas.^{50–53} A variety of monoclonal antibody drugs have been in clinical trials, with small molecules used to target this family of receptors.^{54–56} Although these drugs have had a reasonable toxicity profile, their overall efficacy in regard to either tumor response or prolongation of survival has yet to be proved in pediatrics. Small-molecule inhibitors such as erlotinib, gefitinib, and lapatinib have also been fairly extensively tested against different types of pediatric brain tumors with some hints of efficacy, especially in specific subsets of patients, but no clear benefit in any specific tumor type.

Vascular endothelial growth factor, which comprises three receptors, has been identified as a potential target means to control tumor growth.⁵⁷ Vascular endothelial growth factor and vascular endothelial growth factor receptor increase with hypoxia, thus contributing to further angiogenesis, and act as another means to enhance tumor growth (oxygen tension is lower in rapidly progressing tumors than in normal tissue environments).⁵⁸ Monoclonal antibodies and small-molecule inhibitors of vascular endothelial growth factor ligands and receptors are in active development. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been approved for the treatment of recurrent malignant gliomas in adults.⁵⁹ Multiple studies have been undertaken in pediatrics without clear benefit in trials of adult malignant glioma or brain stem glioma.⁶⁰ There is evidence of efficacy of bevacizumab used in combination with irinotecan for pediatric low-grade gliomas.⁶¹ Some anti-angiogenic drugs have caused significant toxicities, such as difficult-to-control hypertension and proteinuria. A major risk associated with vascular endothelial growth factor receptor drugs, as well as possibly other growth factor receptor inhibitors affecting vasculature, has been intratumoral hemorrhage. To date, this risk has not been rate-limiting in pediatrics but remains significant nonetheless.

Downstream signal transduction pathways have also been targeted in pediatric brain tumors, especially the RAS/mitogen-activated protein kinase pathway, which plays an important role in tumor cell proliferation and survival.⁶² This RAS/RAF/MEK/ERK pathway offers a multitude of targets.⁶² Farnesyl transferase inhibitors, which inhibit the post-translational modification of RAS, have been studied but have not been found to be particularly effective.^{63,64} This may be because they are not selective as to the type of RAS abnormality in the tumor or do not adequately penetrate the tumor. RAF inhibitors, such as sorafenib, are in clinical trials.⁶⁵ Many RAF inhibitors actually are really multi-kinase inhibitors with activity against a variety of signal transduction targets. Although initially it was believed that drugs with great specificity would be most effective, there is a school of thought in developmental therapeutics that agents targeting multiple pathways, so-called multi-kinase inhibitors or “dirty kinase” inhibitors, may be even more effective. Sunitinib, like sorafenib, is a multi-kinase inhibitor that is in clinical trials.⁶⁶

The MEK inhibitors are still another class of drugs that are being actively evaluated. Because of the findings of *BRAF* oncogene activation in a high proportion of grade I (pilocytic) astrocytomas, there is significant interest in using such inhibitors in pediatrics.^{67,68} The phosphatidylinositol 3-kinase/protein kinase/mammalian target of rapamycin (mTOR) pathway is still another pathway being actively targeted in pediatric brain tumors.^{69,70} There has been enthusiasm concerning the use of rapamycin since initial experience in patients with tuberous sclerosis who harbored giant cell astrocytomas demonstrated an excellent response rate to rapamycin or a similar mTOR inhibitor drug, RAD001.⁷¹ How well this type of activity can be generalized to other brain tumors is under active study. Drugs specifically targeting P13 kinase activity are early in study, as are mTOR/P13k dual inhibitors.

The sonic hedgehog pathway seems to play a significant role in the pathogenesis of subsets of medulloblastomas. Sonic hedgehog inhibitors are actively being studied in this tumor type, and there is interest in potentially evaluating the efficacy of these drugs in other CNS tumors.⁷² Similarly, the Notch signaling pathway, which has demonstrated an important role in maintaining neural progenitor cells while inhibiting differentiation, has been noted to be dysregulated in gliomas, medulloblastomas, and ependymomas.^{73,74} γ -Secretase is one of the main proteolytic enzymes that cleaves the receptor and activates the Notch cascade. γ -Secretase inhibitors are a means to decrease Notch signaling.

Histone deacetylase inhibitors are being actively explored in pediatric brain tumors.⁷⁵ Histone deacetylase is involved in chromatin condensation and epigenetic silencing. Interestingly, one of the more commonly used anticonvulsants, valproic acid, is a histone deacetylase inhibitor.^{76–78} Valproic acid and other drugs, such as vorinostat and desipeptide, are in clinical trials. Thalidomide and a newer analogue, lenolidamide, are being used therapeutically because they exhibit activity against vascular endothelial growth factor as well as effects on basic fibroblast growth factor activity and immunomodulation.^{79,80} Lenolidamide is actively being studied in pediatric low-grade gliomas, and thalidomide has been used in a variety of multi-drug (metronomic) anticancer regimens.

Still another potential biological agent is retinoic acid, which acts as a tumor maturation drug.⁸¹ Retinoic acid has effects on both glial and medulloblastoma cells in vitro and is under active study as part of a multiagent approach including more standard chemotherapies in a variety of pediatric brain tumors, especially medulloblastoma.

Cell matrix adhesion is an additional target for pediatric brain tumor therapy.⁸² Integrins are mediators of cell adhesion to the extracellular matrix and play a significant role in the proper migration of cells through both the extracellular and intracellular environment. Integrins also interact with different receptor tyrosine kinases. Cilengitide is an integrin inhibitor that is actively being studied in both pediatric and adult brain tumors.

It should be cautioned that the use of these biological agents is extremely complex.^{6,7} Multiple feedback pathways exist, and it is likely that these agents will have to be used in combination with other biological agents or possibly more standard chemotherapy if they are to play a major role in the treatment of pediatric brain tumors. Specific subtypes of tumors that may have simpler molecular cascades, such as low-grade gliomas, may be more responsive to these biological agents used singly or in simple combinations. How these agents are best used in combination with conventional chemotherapy or radiation therapy is still being elucidated. Given that many of these same pathways are involved in normal brain development, the use of inhibitors has to be closely monitored because of their potential to cause neurodevelopmental toxicities.

50.5 Treatment of Specific Tumor Types with Chemotherapy

50.5.1 Medulloblastoma

Among all patients with childhood primary CNS tumors, the greatest experience with the use of chemotherapy has been in those with medulloblastoma. Prospective randomized studies have demonstrated that children with medulloblastoma can be broadly separated into two risk groups. New molecular markers, however, may change risk stratification significantly in the future.^{1,8,9,83} After treatment with surgery and radiotherapy, children with disseminated disease at the time of diagnosis, and possibly those whose tumors are large and involve the brainstem or are not amenable to total resection, have a poor prognosis, with an overall survival rate after radiation therapy alone of approximately 30 to 40% at 5 years (poor-risk patients). In contradistinction, those patients with localized disease at the time of diagnosis and whose tumors are amenable to aggressive resection have an approximately 50 to 60% survival rate at 5 years (average-risk patients). The addition of chemotherapy during and after radiotherapy has appeared to raise survival rates approximately 20% for both subgroups.

This has led to a generation of studies in which children with poor-risk medulloblastoma were treated with chemotherapy more aggressively in an attempt to improve survival, whereas patients with average-risk disease were treated according to protocols combining radiotherapy and chemotherapy, primarily intended to reduce the amount of radiotherapy given in an attempt to decrease the late effects of treatment. There is also a strong rationale for using chemotherapy as primary therapy for

Table 50.3 Children's Oncology Group ongoing or recently completed studies of chemotherapy for brain tumors

Tumor type	Study type	Chemotherapy	Radiotherapy
Average-risk medulloblastomas	Phase III	During and post-RT: VCR, CPDD, CCNU, Cyclo, VP-16	CSRT: 2,400 cGy versus 1,800 cGy; 5,500 cGy posterior fossa versus tumor site RT
Poor-risk medulloblastomas	Phase III	Carbo during RT versus no Carbo with and without retinoic acid	CSRT: 3,600 cGy; 5,940 cGy local RT
Infantile malignant tumors	Phase I/II	High-dose chemotherapy with Cyclo, VCR, CPDD, VP-16, and thiotepa/carboplatin with PSCR with and without MTX	? Post-Rx RT
Low-grade gliomas	Phase III	Carbo/VCR versus CCNU, PCB, 6-TG, VCR	No RT
Low-grade gliomas	Phase II	Carbo/VCR/temozolomide	No RT
Ependymomas	Phase II	Pre-RT, second-look surgery: Carbo, VCR, VP-16, CPDD, Cyclo	Local RT
Ependymomas	Phase III	Carbo, VP-16, Cyclo versus no chemo for anaplastic post-RT	Local RT
High-grade gliomas	Phase II	Pre-RT chemotherapy/ biological therapy	Local RT
Nongerminomatous germ cell tumors	Phase II	Pre-RT ifosfamide, Carbo, VP-16, ifosfamide, thiotepa	?

Abbreviations: Carbo, carboplatin; CPDD, cisplatin; CSRT, craniospinal RT; Cyclo, cyclophosphamide; MTX, methotrexate; PCB, procarbazine; PSCR, peripheral stem cell rescue; RT, radiotherapy; 6-TG, 6-thioguanine; VCR, vincristine; VP-16, etoposide.

some children with medulloblastoma (especially very young children) to allow deferral and, occasionally, avoidance of radiotherapy (► Table 50.3).

Recurrent Disease

Multiple reports have documented the objective response of recurrent medulloblastoma to a variety of different chemotherapeutic agents, including cisplatin (CPDD), carboplatin, cyclophosphamide, and etoposide, both singly and in combination regimens.⁸⁴⁻⁹¹ However, despite response rates as high as 80% in some studies, durable survival has been rarely documented after conventional doses of chemotherapy. In addition, there are few, if any, long-term survivors noted in series describing children who failed initial treatment with surgery and craniospinal radiotherapy treated with conventional doses of chemotherapy. High-dose chemotherapy supplemented with autologous bone marrow rescue has been used in children with recurrent medulloblastoma.^{22,23,92-95} A high rate of response has been documented in such studies; however, preliminary studies also showed a high rate of treatment-related morbidity. For example, the combination of high-dose thiotepa, etoposide, and carboplatin was used in 23 patients with recurrent medulloblastoma.^{22,23,92} Three patients in this series died of treatment-related toxicity. However, three patients survived without evidence of progression at a median of 36 months from treatment (range, 10 to 63 months). Those patients who did the best after high-dose chemotherapy were those who had minimal residual disease before the use of chemotherapy and no evidence of leptomeningeal dissemination. Other centers, using other high-dose chemotherapeutic regimens, have not reported as many patients with long-term disease control.⁹³⁻⁹⁶ It is likely that even if high-dose chemotherapeutic regimens are documented to be efficacious in some children with recurrent medulloblastoma, the autologous bone marrow rescue approach will be replaced by studies using high-dose chemotherapy supported by peripheral stem cell rescue.

Biological therapy for patients with recurrent medulloblastoma has primarily focused on the use of sonic hedgehog inhibitors, and responses, although primarily transient, have been noted to date.⁹² Notch pathway inhibitors have also been used.^{73,74}

Newly Diagnosed Disease

Based on studies that demonstrated objective responses to chemotherapy in children with recurrent medulloblastoma, post-surgery trials have been undertaken to evaluate the efficacy of chemotherapy, when added to radiotherapy, for children with newly diagnosed disease (► Table 50.4).⁹⁷⁻¹¹²

Two large prospective randomized trials were performed independently by the Children's Cancer Group (CCG) and the International Society of Pediatric Oncology (SIOP).^{1,83} In both studies, patients were randomized to receive radiation therapy alone (3,600 centigray [cGy] of craniospinal irradiation plus local tumor boost to a total dose of 5,400 to 5,600 cGy to the tumor site) or identical radiation therapy plus vincristine (VCR) during the radiation and postradiation therapy cycles of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and VCR. For children in the CCG trial, the postradiation chemotherapy regimen also included prednisone. These trials demonstrated for the first time a statistical benefit for the addition of chemotherapy in children with poor-risk posterior fossa medulloblastoma. In the CCG trial, the estimated 5-year progression-free survival (PFS) rate was 59% for children treated with irradiation and chemotherapy and 50% for those who were treated with irradiation alone. However, in patients with a larger tumor bulk at the time of initial surgery and those with the most extensive tumor, there was a demonstrable benefit from the addition of chemotherapy because the event-free survival (EFS) rate was 48% for those receiving chemotherapy, whereas it was 0% for those treated with radiation alone.

While these prospective randomized trials were being performed, other single-institution trials were also being

Table 50.4 Selected adjuvant chemotherapy trials in children with medulloblastoma

Study (No. of patients)	Type of trial	Dose of CSRT (cGy)	Drugs used	Outcome
McIntosh et al ⁹⁷ (21)	Single arm; all risks	WB 3,925; spinal 3,300	VCR; Cyclo	PFS 5 years 81%
Evans et al ¹ (179)	Randomized; all risks	WB 3,600; spinal 3,600	CCNU/VCR; prednisone versus RT alone	PFS 5 years 60%, w/CHT (high-risk 46% CHT versus 0% no CHT)
Tait et al ⁸³ (251)	Randomized; all risks	WB 3,500–4,500; spinal 3,000–3,500	CCNU; VCR versus RT alone	PFS 5 years 53%
Bailey et al ¹⁰² (364)	Randomized; all risks	WB 3,500; spinal 3,500 versus WB 2,500; spinal 2,500	Pre-RT VCR; PCB; MTX versus VCR; CCNU post-RT	EFS 5 years pre-RT plus no post-RT 2,500 cGy 41% ± 8%
Packer et al ^{98,99} (63)	Prospective; nonrandomized; high-risk	WB 3,600/2,400; spinal 3,600/2,400	Post-RT CCNU; VCR; CPDD	PFS 5 years 85% ± 6%
Packer ¹⁰¹ (65)	Prospective; nonrandomized; average-risk	WB 2,340; spinal 2,340	Post-RT CCNU, VCR; CPDD	PFS 5 years 79% ± 7%
Zelzer et al ¹⁰⁰ (203)	Randomized; high-risk	WB 3,600; spinal 3,600	Pre RT 8-in-1 versus post-RT CCNU; VCR	PFS 5 years 63% ± 5% Post-RT versus 45% ± 5% pre-RT
Kortmann et al ¹⁰⁵ (156)	Randomized; all risks	WB 3,520; spinal 3,520	Pre-RT Ifos; VP-16; MTX, CDDP; ara-C versus VCR; CCNU; CPDD post-RT	EFS 3 years 65% pre-RT versus 78% post-RT
Taylor et al ¹⁰⁷ (217)	Randomized; average-risk	WB 3,500; spinal 3,500	Pre-RT VCR; VP-16; Carbo; Cyclo	EFS 5 years 71.6% (74.2% for pre-RT versus 54.8% for RT)
Packer et al ¹⁰⁹ (420)	Randomized; average-risk	CSRT 2,340	Post-RT Cyclo, CPDD, VCR versus CCNU, CPDD, VCR	EFS 5 years 81% ± 2% OS 86% ± 9%
Carrie et al ¹¹¹ (136)	Average-risk	CSRT 2,500	Pre-RT 8-in-1; post-RT Carbo/VP-16	PFS 5 years 73.8% ± 7.6%
Gajjar et al ¹¹⁰ (134)	All risks	Risk-adapted: 2,340 for average-risk; 3,600–3,960 for high-risk	Post-RT Cyclo; CPDD; VCR plus stem cell	PFS 5 years 85% average- risk; 70% high-risk

Abbreviations: 8-in-1, 8-drugs-in-1-day therapy; ara-C, cytosine arabinoside; Carbo, carboplatin; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CDDP, CPDD, cisplatin; CHT, chemotherapy; CSRT, craniospinal radiotherapy; Cyclo, cyclophosphamide; EFS, event-free survival; Ifos, ifosfamide; MOPP, mechlorethamine, vincristine, prednisone, procarbazine; MTX, methotrexate; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; PCB, procarbazine; post-RT, after RT; VCR, vincristine; VP-16, etoposide; WB, whole brain.

completed. McIntosh and colleagues⁹⁷ reported that 81% of 21 children treated with postradiation therapy cyclophosphamide and VCR were alive and free of disease at a median of 6 years after diagnosis. Packer and colleagues reported that in a three-center trial evaluating 63 children with posterior fossa medulloblastomas, the PFS rate at 5 years was 85.6%.^{98,99} For eligibility in the latter study, children had to be older than 3 years and must have had subtotal resection, evidence of metastatic disease at the time of diagnosis, and/or brainstem involvement. Patients with metastatic disease at the time of diagnosis had a

5-year PFS rate of 67.15% versus 90.6% for those with localized disease.

A study completed by the CCG prospectively treated children who had so-called poor-risk disease with craniospinal and local boost radiotherapy and concomitant VCR chemotherapy during the radiation and eight 6-week cycles of postradiation CCNU and VCR and CPDD, or with 8-drugs-in-1-day therapy for two cycles before irradiation, then craniospinal and local boost radiation, then eight postradiation therapy cycles of 8-drugs-in-1-day therapy.¹⁰⁰ The 3-year EFS rate for the group as a whole

was 57%. However, those children who received the control arm of CCNU and VCR had a statistically higher 5-year EFS rate than did those who received pre- and postradiation 8-drugs-in-1-day therapy (3-year PFS rates of 62.8% vs. 48.8%). A multicenter randomized trial performed by the SIOP that involved 364 children with biopsy-proven medulloblastoma could not demonstrate a benefit for the use of preradiation chemotherapy with a regimen of methotrexate, procarbazine, and VCR.¹⁰² A study performed by the German Cooperative Group, in which an even more aggressive approach to preradiation chemotherapy was used, could not show benefit from treatment with chemotherapy. There was also poorer disease control in the children with localized disease who received preradiation chemotherapy than in those treated with radiation plus postradiation CCNU, VCR, and CPDD chemotherapy.¹⁰⁵ In another randomized trial, the Pediatric Oncology Group (POG) compared postradiation nitrogen mustard, VCR, prednisone, and procarbazine as adjuvant therapy with craniospinal irradiation alone.¹⁰² The 5-year EFS rate for the group receiving radiotherapy and chemotherapy was 68%, compared with 57% for those receiving irradiation alone. Given the number of patients entered, however, this difference was not statistically significant.

The results of another SIOP trial, PNET-3, compared the outcomes of patients who had nondisseminated disease treated with radiotherapy alone (3,600 cGy of craniospinal radiation) with the outcomes of patients who received four cycles of preradiation chemotherapy with oral VP-16, VCR, carboplatin, and cyclophosphamide.¹⁰⁸ Overall survival did not differ statistically between the groups, but the EFS rate at 5 years was lower in those who received radiotherapy alone (5-year EFS rate of 74.2% for those receiving radiation plus chemotherapy vs. 59.8% for those who received radiotherapy alone; $p = 0.0928$).

Although prospective randomized studies comparing 3,600 cGy of craniospinal radiotherapy with reduced-dose craniospinal radiotherapy and adjuvant chemotherapy have never been performed, one of the most compelling studies was one by the Children's Oncology Group (COG) that used 2,340 cGy of craniospinal radiotherapy and either of two chemotherapy regimens: CCNU, CPDD, and VCR or cyclophosphamide, CPDD, and VCR.¹⁰⁹ In both treatment arms, VCR was used during radiotherapy. In 379 evaluable patients, the 5-year PFS rate was $86\% \pm 9\%$; there was no difference between the two chemotherapeutic regimens.¹⁰⁹ A study using higher-dose chemotherapy following radiotherapy, supported by peripheral stem cell rescue, demonstrated a similar rate of PFS.¹¹⁰ A French study also demonstrated that the dose of craniospinal radiotherapy could be reduced to 2,400 cGy if chemotherapy was added.¹¹¹

These studies, taken in total, suggest that adjuvant chemotherapy is of benefit in children with medulloblastoma. The trials, to date, that have used preradiation chemotherapy have shown no clear advantage for the addition of such chemotherapy in children with more extensive disease at diagnosis and poorer survival for those with average-risk disease compared with immediate postoperative radiotherapy and adjuvant chemotherapy during and after radiotherapy.¹¹² Preradiation chemotherapy may be better than treatment with radiotherapy alone for patients with disseminated disease, but it is unclear whether it is as effective as treatment with radiotherapy plus chemotherapy during or after irradiation. It is paradoxical that children with average-risk disease treated with radiation alone

seem to have no better survival rates or, in some studies, poorer survival rates than do children with poor-risk disease treated with radiation plus chemotherapy.¹⁰⁸

For children with high-risk medulloblastoma, another potential use of chemotherapy is to intensify treatment, either by administering chemotherapy during radiation (carboplatin) to act as a radiosensitizer or by increasing the dose of postradiation chemotherapy by means of peripheral stem cell rescue. Both approaches have shown possible benefit.

Treatment of Infants

Infants are yet another subset of children with medulloblastoma who have been extensively treated with chemotherapy.^{113,114} Most studies indicate that the prognosis for children in whom medulloblastoma is diagnosed in the first 3 to 4 years of life is poorer than that in older children, independently of whether they are treated with radiation alone or radiation in conjunction with chemotherapy. Because cranial irradiation in young children has been associated with severe adverse delayed toxicities, including intellectual deterioration and endocrinologic (especially growth) sequelae, multiple studies dating back to the 1970s have utilized postsurgical chemotherapy, with delayed or no radiotherapy, for infants with medulloblastoma. In an early study, the use of mechlorethamine, Oncovin (VCR), procarbazine, and prednisone (MOPP) chemotherapy in 13 children younger than 36 months of age with medulloblastoma resulted in a PFS rate of 55%.¹¹⁵ The largest early experience has been that of the POG, which used a four-drug regimen of VCR, cyclophosphamide, CPDD, and etoposide in children younger than 3 years of age with medulloblastoma until they were 36 months of age, or for at least 12 months.⁵ In this protocol, delayed irradiation was given upon completion of chemotherapy, and the median time to relapse in patients with medulloblastoma was 9 months; 34% of patients remained progression-free for a median of 2 years from diagnosis. No patient had a relapse beyond 26 months from diagnosis, raising the issue of the necessity of irradiation in those with a complete response. The CCG has used the 8-drugs-in-1-day chemotherapy regimen for children younger than 18 months of age with newly diagnosed medulloblastoma.¹¹³ In this study, radiation therapy was not routinely employed in those children with a complete response, and the 3-year PFS rate was 22%. The German Cooperative Group has used four cycles of an aggressive regimen of ifosfamide, methotrexate, CPDD, VCR, and intravenous cytosine arabinoside (ara-C) for infants with medulloblastoma.¹¹⁶ The treatment of patients with localized disease at diagnosis resulted in a 2-year disease-free survival rate of 92% without radiotherapy. In contrast, in all patients with disseminated disease, their disease ultimately progressed during or after chemotherapy treatment.

In an even more aggressive approach, investigators at Memorial Sloan-Kettering Cancer Center in New York City and participating institutions treated children younger than 3 years who had localized medulloblastoma and children between 3 and 6 years of age who had disseminated medulloblastoma with five cycles of induction chemotherapy (CPDD, high-dose cyclophosphamide, etoposide, and VCR) followed by a consolidation cycle of myeloablative chemotherapy (thiotepa, etoposide, and carboplatin), supported by autologous bone marrow rescue.¹¹⁷ In 13

patients, the 5-year EFS and overall survival rates were 51% and 61%, respectively.

Still another approach is the addition of intrathecal chemotherapy to systemic chemotherapy. Infants with nondisseminated medulloblastoma treated with high-dose intravenous and intraventricular methotrexate and cytosine arabinoside, coupled with other systemic chemotherapeutic agents, demonstrated a nearly 60% 5-year PFS rate without receiving radiotherapy.^{118–120} This study and a subsequent follow-up study achieved a disease-free survival rate of greater than 80% for those with nodular or desmoplastic medulloblastoma, demonstrating both the better prognosis for the subgroup of patients with that variant of medulloblastoma and that some infants can be treated with chemotherapy alone after surgery. Methotrexate has been associated with a high rate of leukoencephalopathy, raising issues over the long-term benefits of such approaches. The ability of chemotherapy alone to control disseminated disease in infants has never been shown. Other approaches are coupling biological agents, including retinoic acid and SAHA (suberoyl anilide hydroxamic acid), with multiagent chemotherapy to improve disease control.

50.5.2 Other Primitive Neuroectodermal Tumors

The chemotherapy used for children with primitive neuroectodermal tumors (PNETs) arising outside the posterior fossa, including pineoblastomas, has mirrored that used for children with medulloblastomas. Data suggest that children with non-posterior fossa PNETs have a poorer prognosis than those with medulloblastomas, possibly because of their younger age at the time of diagnosis or because such tumors (especially pineoblastomas) are frequently disseminated early in the course of illness.^{121–123} Also, non-posterior fossa tumors are genomically different from medulloblastomas.

The role of adjuvant chemotherapy for children with non-posterior fossa PNETs has not been well demonstrated.^{121,122} This is partially due to the relatively small numbers of patients available for study. In the CCG trial comparing pre- and post-radiation chemotherapy with the 8-drugs-in-1-day regimen versus treatment with radiation therapy plus CCNU and VCR, children with both pineal PNETs and non-posterior fossa, non-pineal PNETs were treated. For the 44 patients with supratentorial PNETs, the PFS rate was 45.8%. In addition, 25 children with pineal tumors were treated. Eight were younger than 18 months and were nonrandomly treated with the 8-drugs-in-1-day chemotherapy regimen. The remaining 17 patients were randomized between the two treatments. All infants in this study developed progressive disease at a median of 4 months from the start of treatment. In the 17 older patients, the overall 3-year PFS rate was 61.13%. The numbers in this study are too small to evaluate the relative efficacy of either of the two adjuvant chemotherapy regimens. In the SIOP study, 25 children with supratentorial PNETs were treated with chemotherapy alone, and 24 had a relapse at a median of 5.5 months. In a study in older children, radiotherapy plus CCNU, VCR, and CDDP chemotherapy resulted in an approximately 50% rate of disease control.¹²⁴ High-dose chemotherapy with peripheral stem cell rescue using cyclophosphamide, CPDD, and VCR following

radiotherapy has also been tried in this population, with at least evidence that such an approach is feasible.¹⁹ Given the poor outcome of children with non-posterior fossa PNETs, most investigators are using some form of chemotherapy in addition to radiation therapy.

50.5.3 High-Grade Gliomas

The issue of the efficacy of chemotherapy for malignant gliomas in childhood remains somewhat unsettled.³ To date, chemotherapeutic trials for pediatric malignant gliomas have largely been initiated based on the encouraging results observed for a particular drug or regimen first investigated in adult malignant gliomas. However, it is now becoming clear that adult GBMs are molecularly heterogeneous and quite distinct from pediatric lesions.^{125,126} Thus, it is very likely that future pediatric trials will need to be designed and tailored more specifically for the molecular targets uniquely represented in the pediatric form of the disease. The molecular genetic alterations of both childhood and adult malignant gliomas are still being elucidated, but emerging evidence now demonstrates that malignant astrocytic tumors arising in childhood are more likely to have *TP53* mutations and thus a genetic composition different from that of the neoplasms of adulthood, which are believed to go through a cascade of genetic changes as they progress from low-grade to high-grade malignancies.¹²⁷ This may in part explain the differences, if they exist, between the sensitivities to chemotherapy of adult and pediatric malignant gliomas. For example, adult patients with GBM demonstrated a clear survival benefit with the addition of temozolomide to standard-dose irradiation; however, a similar benefit was not demonstrated in an identical pediatric malignant glioma trial.¹²⁸ Molecularly targeted therapy against alterations more commonly observed in high-grade pediatric gliomas, such as *PDGFRA* amplification, are under way at some centers. Other strategies, such as the combination of anti-angiogenesis inhibitors or other novel biological agents with radiation, are being investigated. Clinical trials, as noted in ► Fig. 50.1, are ongoing to better define the role of chemotherapy in high-grade glioma management.

Recurrent Disease

At the time of recurrence, malignant gliomas may transiently respond to chemotherapeutic agents. Interpretations of chemotherapy trials are difficult, especially in adult series, because many trials combine patients with objective neuroradiographic response together with those who have disease stabilization, considering both groups as “responders.”^{129–131} The nitrosoureas singly or in combination with other drugs, such as procarbazine and VCR, have been the most extensively studied drugs in adult Phase II trials; overall objective response rates usually have ranged from 10 to 20% (although some report transient benefit in as many as 75% of patients). Median time to progression in most series, which may be a better marker of efficacy, is usually less than 6 months, with most series documenting disease progression by 20 to 25 weeks after the initiation of treatment. Studies in purely pediatric populations with recurrent malignant gliomas have been undertaken less commonly. Drugs that have been evaluated include VCR, procarbazine, intravenous etoposide, oral etoposide, BCNU, CCNU, CPDD,

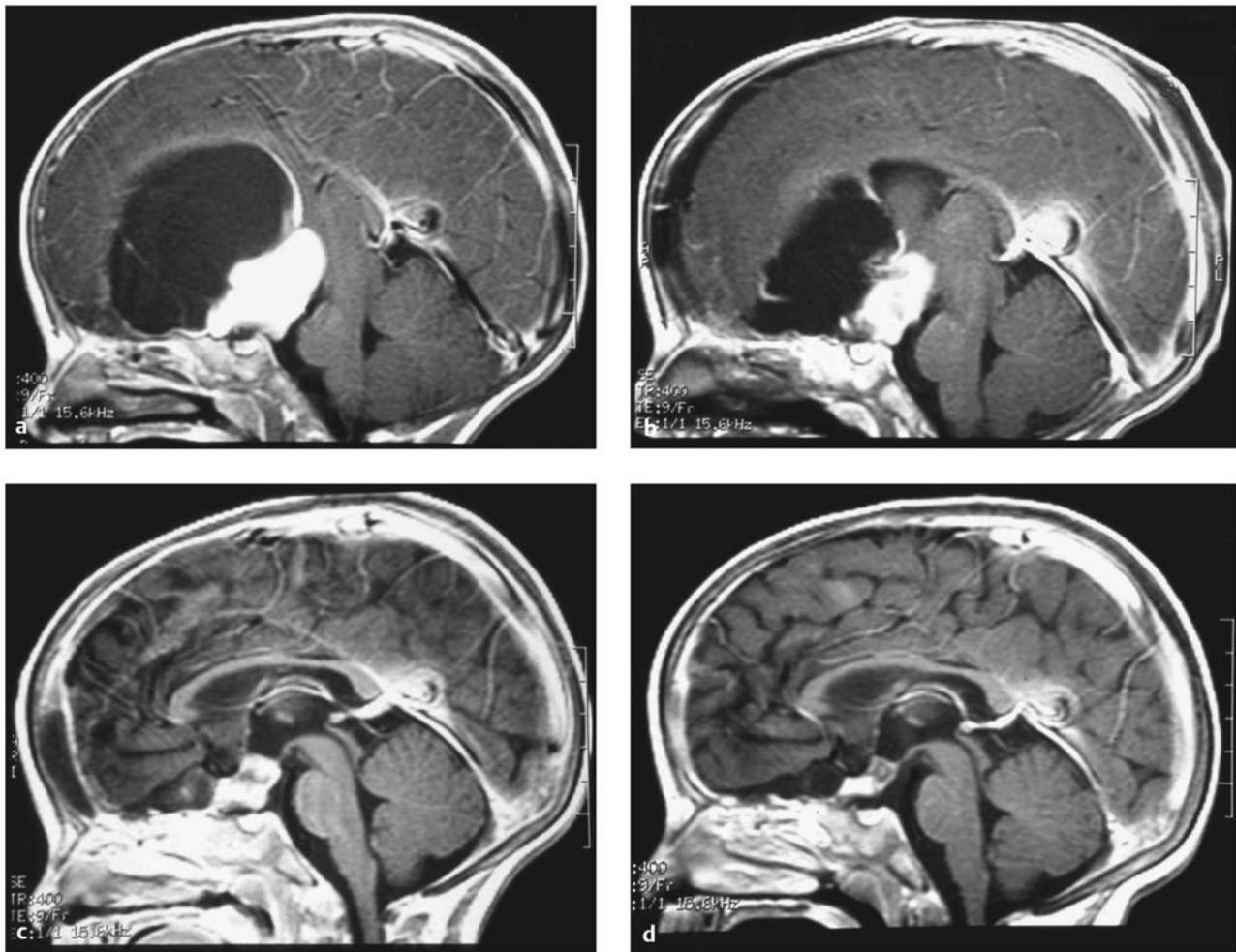


Fig. 50.1 Sagittal magnetic resonance imaging after gadolinium (a) at diagnosis, (b) following surgery, (c) at 3 months, and (d) at 12 months after treatment with carboplatin and vincristine in an 11-month-old child without neurofibromatosis with a diencephalic pilocytic astrocytoma.

cyclophosphamide, carboplatin, irinotecan, and thiotepa as single agents or in combination with another agent, such as ifosfamide or high-dose cytosine arabinoside.^{132–150} These studies have shown objective response rates ranging from 0 to 50%, with most studies reporting tumor shrinkage in 10% of patients or fewer. As in adult trials, even in those series reporting a higher rate of response, the median time to progression has been less than 1 year and usually 6 months or less.

Temozolomide is an oral alkylating agent that has been well tolerated and has shown promising but mixed results in adults and children with recurrent high-grade gliomas.^{151–153} In adult trials, objective responses plus stable disease were reported in as many as 67% of patients with recurrent grade II tumors. For patients with GBM, similar overall “responses” were noted, but the duration of response was shorter. Experience in pediatric patients has been less extensive, with a greater variability noted in pediatric series, with objective responses ranging from 0% in a CCG series to as high as 50% in a smaller limited-institution trial.¹⁵¹ One approach to increase the efficacy of temozolomide and other drugs that alkylate DNA in the O6 position, such as the nitrosoureas and procarbazine, is to couple such treatments with drugs that bind to the DNA repair protein O6-alkylguanine

DNA-alkyltransferase. One such drug is O6-benzylguanine. Despite encouraging preliminary data, the most recent pediatric clinical trial for refractory high-grade gliomas using the combination of temozolomide and O6-benzylguanine failed to demonstrate efficacy.¹⁵⁴

There has been interest in the use of higher doses of chemotherapy for children with malignant gliomas supplemented by either autologous bone marrow rescue or peripheral stem cell rescue.^{22,155–157} Thiotepa and etoposide have been used at high doses for children with malignant gliomas. Objective responses to therapy were noted in 6 of the first 10 patients treated. Later studies combining high-dose BCNU with thiotepa and etoposide or high-dose carboplatin with thiotepa and etoposide disclosed a similar overall response rate in a larger group of patients. These studies also encouragingly disclosed a small subgroup of children with prolonged survival, including children with anaplastic gliomas and those with GBMs. These results were tempered by a toxic mortality rate of nearly 20% in the preliminary studies. Other groups using different chemotherapeutic agents, such as busulfan and thiotepa or melphalan-based regimens, have not been able to demonstrate such high response rates or prolonged responses to chemotherapy.^{22,155–157} The reasons for

these disparities in studies are unclear; however, it does seem that patients with minimal residual disease before treatment with high-dose chemotherapy (those with tumors that could be debulked before chemotherapy) were the most likely to derive a prolonged benefit from treatment.

Newly Diagnosed Disease

Despite multiple single-institution trials and prospective randomized studies, the value of adjuvant chemotherapy for adults with malignant gliomas is far from dramatic. Chemotherapy for adults, when given as an adjuvant with or after radiation therapy, produces a modest prolongation in median survival but has not clearly been shown to improve the likelihood of long-term survival.^{158–163} A meta-analysis of major adjuvant chemotherapy trials concluded that there was a 10% increase in survival at 1 year and an 8.6% survival advantage at 2 years for adults who had GBM treated with chemotherapy and radiotherapy compared with those treated with irradiation alone.^{164,165}

The study that has suggested most strongly that adjuvant chemotherapy is of benefit for children with high-grade gliomas was completed by the CCG in 1982.³ In this trial, the addition of CCNU and VCR chemotherapy, during and after radiotherapy, increased survival compared with treatment with radiation alone. Of the children in this randomized trial who received radiotherapy and adjuvant chemotherapy, 46% were alive and free of disease 5 years following treatment versus 18% of those treated with postsurgery radiotherapy alone. The benefit of chemotherapy was statistically significant for children with GBM.

In a follow-up study, the CCG compared pre- and postradiation chemotherapy with the 8-drugs-in-1-day regimen versus therapy with irradiation and CCNU and VCR.¹⁶⁶ No survival advantage was shown for the children treated with pre- and post-radiation 8-drugs-in-1-therapy in comparison with those treated with adjuvant CCNU and VCR. Overall, the survival rates for children with anaplastic gliomas and those with GBM were somewhat lower in the most recent CCG trial, but approximately 30% of children with anaplastic gliomas and 20% of children with GBM were alive and free of disease 5 years following treatment. A statistical comparison of these two trials showed no difference in overall survival between them.¹⁶⁷ A more recent review of this information suggested that some of the children considered to have high-grade gliomas in the first CCG trial actually had low-grade gliomas. However, even when the pathologic materials were reviewed again, there was a statistical benefit for the addition of CCNU and VCR for children with GBM.

Given the equivocal results of adjuvant trials and the preliminary results of high-dose chemotherapy for recurrent high-grade glioma, studies are presently ongoing using high-dose chemotherapy either before or following radiation therapy for children with anaplastic gliomas (primarily subtotally resected tumors) and children with GBM. A CCG trial that used couplets of agents, including cyclophosphamide and VCR, ifosfamide and VCR, and carboplatin and VCR, before irradiation demonstrated an overall poor objective response rate of less than 20%.¹⁶⁸ Alternatively, trials of chemotherapy during radiation therapy with agents like temozolomide in patients with newly diagnosed disease are ongoing. However, temozolomide alone given

concurrently with radiation on a daily low-dose schedule followed by a standard dose and scheduled maintenance temozolomide failed to improve survival in the most recent COG trial for newly diagnosed pediatric malignant gliomas.¹²⁸ Newer biological agents, such as inhibitors of tyrosine kinase receptors (anti-EGFR and anti-PDGFR), epigenetic modifying agents such as histone deacetylase (HDAC) inhibitors, anti-angiogenesis agents (e.g., bevacizumab, cilengitide), and cell signal-disrupting agents, have also been coupled with irradiation in attempts to improve disease control.

50.5.4 Brainstem Gliomas

The majority of children with brainstem gliomas have diffuse infiltrating lesions that primarily involve the pons and result in death within 18 months of diagnosis. Because of this poor survival rate, chemotherapy has been used in children with both newly diagnosed and recurrent brainstem gliomas. Such studies are still ongoing, but there has been increased interest in using chemotherapy during radiotherapy for patients with newly diagnosed disease.

Recurrent Disease

At the time of recurrence, a variety of single agents investigated in patients with high-grade gliomas (e.g., intravenous carboplatin, cisplatin, and etoposide; oral thiopeta and CCNU) have resulted in responses in only 0 to 20% of patients.^{169–173} Temozolomide has also been used, with disappointing results. Furthermore, in the majority of cases, even if partial tumor shrinkage occurred, the response was relatively short. Oral etoposide resulted in a response in 4 of 12 children with recurrent brainstem gliomas.¹⁶⁹ In addition, a variety of drug combinations have been tried without clear benefit.

Newly Diagnosed Disease

Adjuvant postradiation chemotherapy has been poorly studied in children with brainstem gliomas. In one of the few randomized prospective studies performed to date, the addition of postradiation CCNU and VCR did not improve the length or frequency of disease-free survival in comparison with radiotherapy alone.¹⁷⁴ The median PFS in this study of 79 children with brainstem gliomas was 7 months for those receiving radiation therapy alone and 6 months for those treated with radiation and chemotherapy.

Chemotherapy has been used before irradiation in an attempt both to identify active agents and to improve survival. One study of cisplatin and cyclophosphamide in 32 children demonstrated that such therapy could be delivered before radiotherapy but resulted in a poor overall response rate (3 of 32, or 9%) with no improvement in survival.¹⁷⁵ Carboplatin given before radiotherapy resulted in responses in 2 of 27 patients; the median overall survival in this series was 9 months.¹⁷¹ In a CCG trial, treatment with cisplatin, etoposide, cyclophosphamide, and VCR or with carboplatin, etoposide, and VCR before irradiation resulted in few objective responses and no apparent improvement in survival.¹⁷⁶ Another trial coupled carboplatin with a bradykinin agonist during radiotherapy to improve drug delivery but did not show apparent improved survival. High-dose,

multiagent chemotherapy, such as that used in protocols designed for patients with high-grade cortical gliomas, has been attempted in this population before irradiation. However, because of inordinate toxicity and a lack of clear efficacy, these studies were aborted.¹⁷³⁻¹⁷⁵ Other studies are evaluating the efficacy of chemotherapy, biological agents, and novel radiosensitizers during and after radiation in attempts to improve survival. To date, no agent has shown clear benefit.

Interferon has been used in children with both recurrent and newly diagnosed brainstem gliomas.¹⁷⁶⁻¹⁷⁸ Nagai and Arai¹⁷⁷ demonstrated objective responses in 8 of 20 patients with recurrent high-grade gliomas after intrathecal or intratumoral infusion of interferon- β . Interferon- β resulted in objective tumor responses in 2 of 9 children with recurrent brainstem gliomas and prolonged disease stabilization in 2 patients in another series.¹⁷⁶ However, a follow-up study of interferon- β , given both during and following irradiation for patients with newly diagnosed brainstem gliomas, did not demonstrate increased efficacy.¹⁷⁸ In this latter study, 32 children were treated, and 30 of 32 developed progressive disease at a median of 5 months from diagnosis. In contrast, a study by Wakabayashi et al¹⁷⁹ treated 16 pediatric patients who had a diagnosis of brainstem glioma with interferon- β , ACNU ([1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride]), and radiation therapy. Of 8 patients in this series with diffuse intrinsic tumors, 7 were reported to have a complete or partial response to treatment, with a median overall survival of 15.7 months. Surprisingly, in the study of Wakabayashi et al, the best survival rate was seen in patients with diffuse intrinsic tumors. The role of interferon- β for patients with brainstem gliomas thus remains unclear, but studies continue to be performed with this agent and other forms of immunotherapy.

50.5.5 Low-Grade Gliomas

Low-grade gliomas constitute the majority of childhood brain tumors. Until the 1980s, chemotherapy was used sparingly in children with recurrent and newly diagnosed low-grade gliomas.^{180,181} Most studies were performed primarily in children with diencephalic tumors. Similar outcomes, in smaller numbers of patients, have been reported in children with tumors in other CNS sites, including the brainstem. For exophytic pilocytic astrocytomas, a variety of drugs demonstrated efficacy against recurrent tumors, although in most cases, these regimens were used in only a small group of patients.¹⁸¹⁻¹⁸⁷ Drugs or drug combinations that have been used and found to be somewhat effective in children with recurrent low-grade gliomas include actinomycin and vincristine, carboplatin alone, carboplatin and vincristine, vinblastine, vinorelbine and carboplatin, etoposide, etoposide and cisplatin, temozolomide, and multidrug regimens, such as TPCV (CCNU, procarbazine, vincristine, 6-thioguanine, and dibromodulcitol). Most studies using single-agent temozolomide, vinorelbine, or carboplatin reported stable disease, although the regimen of carboplatin and vincristine resulted in objective tumor shrinkage in 9 of 19 patients.¹⁸⁶

Biological agents have recently been incorporated into the therapy of recurrent low-grade gliomas. Bevacizumab plus irinotecan demonstrated a 30 to 60% response rate, at times associated with visual or neurologic improvement, in children with multiply recurrent low-grade gliomas.⁶¹ Drugs targeting the

RAS/MAPK pathway are being actively explored, stimulated by the discovery of *BRAF* mutations in the majority of children with pilocytic astrocytomas.⁶² Inhibition of *BRAF* and *MEK*, as well as inhibitors of *mTOR*, are under active study.

Newly Diagnosed Disease

The role of chemotherapy for children with newly diagnosed low-grade gliomas is established, although the optimal regimen remains to be determined. In attempts to decrease the potential long-term sequelae of radiation therapy, chemotherapy has been used to at least delay, if not obviate, the need for radiation therapy. The largest early experience with chemotherapy was with the combination of actinomycin D and VCR.¹⁸⁸ In a series of 30 patients younger than 5 years of age with newly diagnosed, progressive visual pathway gliomas, 80% of the children were shown to have at least disease stabilization while receiving chemotherapy (an overall objective response was seen in 20% of patients). This stabilization lasted for a mean of 3 years and resulted in the requirement for radiation at a median age of 4.5 instead of 1.5 years. Subsequently, the combination of carboplatin and VCR has been widely used for children with newly diagnosed or progressive low-grade gliomas at any site in the nervous system.¹⁸⁷ The overall response rate after treatment with carboplatin and VCR was 60% (► Fig. 50.1). More than 90% of patients, independently of the location of their tumor in the nervous system, experienced at least disease stabilization with this regimen. In a series of 78 patients, the PFS rate with the two-drug regimen was 68% at 3 years, and therapy was shown to benefit both patients with diencephalic tumors and those with progressive low-grade brainstem tumors.

Other agents and drug combinations have been used in patients with newly diagnosed disease. The TPCV combination of CCNU, VCR, 6-thioguanine, procarbazine, and dibromodulcitol demonstrated either stabilization or objective response in 12 of 15 patients with newly diagnosed low-grade tumors.¹⁸⁹ CPDD and etoposide resulted in a 70% response rate in 34 patients with progressive low-grade gliomas and a PFS rate of 78% at 3 years.¹⁹⁰ Similar results have been reported with even more aggressive multiagent regimens containing CPDD and cyclophosphamide used by the French Society of Pediatric Oncology. A COG randomized study in children younger than 10 years of age with progressive low-grade gliomas, comparing the carboplatin and vincristine regimen with the TPCV regimen, found a borderline statistical advantage at 5 years for the TPCV regimen (EFS 35% \pm 4.7% for carboplatin/vincristine vs. 48% \pm 4.8% for TPCV).¹⁹¹ Secondary tumors may be more likely after the TPCV regimen. A recently completed study adding temozolomide to the carboplatin and vincristine regimen has shown impressive 3-year disease control. In all these studies, children with neurofibromatosis type 1 (NF-1) are excluded from the alkylator-based regimens because of concerns over an increased incidence of mutagenesis. Children with NF-1 have a better than 50% rate of disease control at 5 years after treatment with carboplatin and vincristine. A treatment-limiting complication with the carboplatin and vincristine regimen is drug allergy in up to 30% of those being treated.

There is substantial evidence that chemotherapy can result in at least transient disease stabilization and delay the need for radiotherapy. However, the short- and long-term sequelae of

more aggressive regimens, such as hearing loss, an increased risk for infection, and mutagenesis, need to be carefully assessed, especially if disease control is similar with less aggressive chemotherapeutic treatment.¹⁹² This is significant for very young children with large, diffuse tumors. The role for chemotherapy in older children is less clear. There is no evidence to support combining chemotherapy with radiation therapy in children with low-grade tumors.

50.5.6 Oligodendrogliomas

Information on the utility of chemotherapy for children with either newly diagnosed or recurrent oligodendrogliomas is essentially nonexistent. Given the rarity of this tumor in the pediatric population, most studies have included children with oligodendrogliomas either in trials of patients with malignant gliomas or, alternatively, in studies of children with low-grade gliomas. The combination of procarbazine, CCNU, and VCR has demonstrated a high response rate in adults with recurrent malignant oligodendrogliomas.¹⁹³ One report of 37 pediatric patients from a single institution indicated that gross total resection and age older than 3 years correlated with improved PFS, yet neither postoperative chemotherapy nor irradiation was associated with outcome.¹⁹⁴

50.5.7 Ependymomas

The value of chemotherapy for children with ependymomas is unclear. In most series, more than 50% of children with either benign or malignant ependymomas have disease recurrence, and a variety of chemotherapeutic agents have been used in an attempt to control disease. Such therapy is being actively explored in national trials (► Table 50.3).

Recurrent Disease

The nitrosoureas have been variably associated with response in the setting of recurrence. Cisplatin has been reported to result in objective responses in from 30 to 60% of patients at the time of recurrence.^{136,137,143,194} In one study, aggressive treatment with chemotherapy following surgical re-resection and then further chemotherapy resulted in prolonged disease control in approximately 30% of children with locally recurrent ependymomas.¹⁹⁵ Other drugs have shown variable degrees of efficacy.

Newly Diagnosed Disease

In the adjuvant setting, a benefit of chemotherapy has never been shown for children with ependymomas. In a small series of patients, CCNU and VCR during and after radiotherapy did not result in improved survival in comparison with radiation therapy alone.¹⁹⁶ In a prospective randomized trial of 32 children with ependymomas treated with either 8-drugs-in-1-day therapy before and after radiotherapy or with radiotherapy plus adjuvant CCNU and VCR chemotherapy, the 5-year PFS rate was 50% ± 10%, and the type of chemotherapy employed did not affect outcome.¹⁹⁷ A single-arm study using hyperfractionated radiation therapy followed by carboplatin, VCR, ifosfamide, and etoposide chemotherapy suggested an early impressive degree

of disease control, but long-term follow-up has not been reported.¹⁹⁸

The outcome of children with ependymomas seems to depend most on the extent of resection at the time of diagnosis. Patients with totally resected tumors have been reported to have survival rates as high as 70% 5 years after diagnosis. Chemotherapy trials are thus also aimed at seeing whether second-look surgery may be rendered feasible. There appears to be no clear effect of tumor location or histologic grade on outcome in patients with totally resected tumors, although more recent studies suggest that anaplasia may confer a worse prognosis and that completely resected nonanaplastic supratentorial ependymomas may be observed.¹⁹⁹ For this reason, the majority of adjuvant chemotherapy trials are now focusing on patients with subtotally resected tumors or those who have leptomeningeal spread at the time of diagnosis. A CCG trial using preradiation cyclophosphamide, VCR, cisplatin, and etoposide in 37 patients demonstrated an objective response rate of more than 50% and a 3-year EFS rate of 55% ± 9%.²⁰⁰ Preradiation chemotherapeutic studies and postradiation chemotherapy for those with residual tumor are being performed in an attempt to see whether chemotherapy-induced “complete resection” can improve survival, as well as to identify active drug regimens. Most recently, high-throughput methods of screening Food and Drug Administration (FDA)-approved compounds in both *in vitro* and *in vivo* models of ependymoma have yielded possible drug candidates, including 5-fluorouracil.²⁰¹

50.5.8 Germ Cell Tumors

Chemotherapy is an integral component of the treatment of testicular and ovarian germ cell tumors, but it has not been routinely integrated into the management of intracranial germ cell tumors.^{202,203} Because localized germinomas have high response and cure rates after radiation therapy alone, there has been limited experience with chemotherapy used either as an adjuvant after radiotherapy or alone after surgery for patients with newly diagnosed nondisseminated germinomas. Chemotherapy has been used more widely for patients with disseminated germinomas at the time of diagnosis and for the occasional patient who has failed initial surgery and radiation.²⁰⁴ Recently, there have also been attempts to use chemotherapy before radiotherapy in patients with localized disease to allow a reduction in the amount and volume of radiotherapy required for disease control.^{205,206}

The outcome of patients with intracranial nongerminomatous germ cell tumors is quite poor, with most series reporting survival rates of considerably less than 50% at 5 years. These patients have occasionally been treated with chemotherapy, although large groups of similarly treated patients do not exist.

Response has been demonstrated for a variety of individual drugs and drug regimens in patients with germinomas. These drugs include high-dose cyclophosphamide, methotrexate, CPDD, and regimens using the same drugs together with other agents, such as BCNU, procarbazine, bleomycin, VP-16, vinblastine, and actinomycin D.^{204,207} In one series, CPDD was demonstrated to result in rapid tumor shrinkage in 4 of 8 patients with germinomas and teratomas.²⁰⁸ Cyclophosphamide alone or in combination with vinblastine, bleomycin, cyclophosphamide, and CPDD resulted in a complete response in 10 of 11 patients

with newly diagnosed germinomas, including 7 who had disseminated disease at the time of diagnosis.²⁰⁶ The remaining patient had a partial response to treatment. In this study, the dose of radiotherapy to the primary site was reduced from 5,500 to 3,000 cGy, and the craniospinal dose was lowered from 3,600 to 2,000 cGy; 10 of the 11 patients were disease-free at a median follow-up of 47 months. All 4 patients with nongerminomatous germ cell tumors in this series were treated with the multidrug regimen and full-dose craniospinal radiation therapy, but recurrent disease ultimately developed. In a smaller series, carboplatin as a single agent resulted in a high response rate in patients with both localized and disseminated germinomas.

As an outgrowth of these studies, attempts have been made to use chemotherapy alone in children and adults with primary intracranial germ cell tumors. In the largest series to date, 71 children and adults with either germinomas or nongerminomatous germ cell tumors were treated with postsurgery cycles of carboplatin, etoposide, and bleomycin.²⁰⁹ Of 68 patients, 39 had a complete response after four cycles of chemotherapy, 24 had a partial response, 4 had stable disease, and 4 had progressive disease. Of the 29 patients in this series who had less than a complete response after four cycles of therapy, 16 were re-treated with the same three-drug regimen plus high-dose cyclophosphamide. A complete response was ultimately achieved in 10 of these 16 patients. Interestingly, the frequency of response did not differ between the patients with germinomas and those with nongerminomatous germ cell tumors. Tumor recurrence developed in 55% of the patients in this series at a median of 18 months from diagnosis, and there was no clear difference between the patients with germinomas and those with nongerminomatous germ cell tumors. Of the 45 patients with germinomas entered on the protocol, 22 developed tumor progression and 4 died of treatment-related complications. Overall, this PFS rate after chemotherapy alone seems significantly poorer than what has been reported in other series treating patients with radiation therapy alone; however, it is unclear how many patients in this series can be adequately salvaged (or possibly cured) by subsequent radiation therapy.²⁰⁹

Based on these results, it is difficult to make definitive recommendations concerning the use of chemotherapy for patients with intracranial germinomas and nongerminomatous germ cell tumors. Although the information available suggests that these tumors are chemosensitive, it is unclear whether the addition of chemotherapy to radiation results in better survival. There is some suggestion that chemotherapy will allow a reduction in the dose of radiation therapy, especially in those children with disseminated disease. Given the poor outcome of patients with nongerminomatous germ cell tumors, most investigators suggest that chemotherapy be used either before or following radiation therapy. However, the most effective regimen has not yet been determined and is being assessed by multiple investigations, including national studies (► Table 50.3).

50.5.9 Choroid Plexus Tumors

The management of choroid plexus papilloma is usually purely surgical, and there is no documented role for chemotherapy in this disease. The outcome of patients with choroid plexus carcinoma is less favorable, and chemotherapy has been employed both at the time of tumor recurrence and at the time of

diagnosis. At the time of tumor recurrence, responses can be documented to a variety of agents, including VP-16. For patients with newly diagnosed disease, the best reported outcome after the use of chemotherapy has been following the treatment of infants and young children with surgery and cyclophosphamide, VCR, VP-16, and cisplatin.²¹⁰ However, the majority of children who experienced prolonged disease remission after such treatment had total resections, and it is unclear whether chemotherapy increased the likelihood of disease control. In one study, the use of ifosfamide, carboplatin, and etoposide appeared to facilitate second-look surgery and avoid radiation, with 8 of 13 patients experiencing a median long-term survival of approximately 7 years.²¹¹

50.6 Chemotherapy and Infant Tumors

As outlined in previous sections, chemotherapy has recently been extensively used in infants with both malignant and benign tumors. The widest experience has been with the use of chemotherapy in young children with newly diagnosed medulloblastomas and other PNETs. In patients with such tumors who have residual disease after surgery, a variety of single-drug and multiple-drug regimens have been shown to shrink tumors, but fewer than one-half of patients attain a complete response after induction chemotherapy (independently of the type of regimen used).^{113,114,149–152,212,213} In patients with less than a complete response, tumors usually recur within months of diagnosis. At the time of tumor recurrence after chemotherapy, both radiation therapy and high-dose chemotherapy may once again induce remission. In one study, after initial chemotherapy failure, reinduction was successfully achieved with the use of higher-dose busulfan-based chemotherapy followed by some form of radiotherapy.⁹⁶ For patients with local failure, radiotherapy was delivered locally, and a high percentage of patients had prolonged disease control. In contrast, when failure was disseminated, treatment with high-dose chemotherapy followed by craniospinal radiotherapy was unsuccessful in controlling disease.

An effective regimen that will result in a higher than 50% complete response rate in patients with residual disease or disseminated disease at the time of diagnosis has not been identified. The most appropriate management for patients with a complete response after initial chemotherapy, or with no residual disease after surgery and a continued complete absence of tumor after induction chemotherapy, is unclear and controversial. Some investigators have recommended high-dose chemotherapy supplemented by either autologous bone marrow rescue or peripheral stem cell rescue as consolidation therapy.¹¹⁷ Others have recommended radiation therapy (either craniospinal or focused). Several groups have advocated the use of chemotherapy after initially incomplete resection of choroid plexus carcinomas as a way to diminish tumor bulk and vascularity, and (it is hoped) permit a second-stage complete resection. Maintenance chemotherapy is also being employed in patients without residual disease after surgery and induction treatment.

Surprisingly, some studies have suggested that infants with malignant gliomas fare as well as, if not better than, infants

with medulloblastomas after treatment with chemotherapy alone. The numbers of patients treated with chemotherapy alone (and therefore the number of studies) are quite small, but response rates as high as 60% have been reported. It has been postulated, but not proved, that infants with malignant gliomas may harbor tumors that are biologically different from those of older children and adults with histologically similar lesions.

The treatment of infants with ependymomas remains quite problematic. In one series, the regimen of cyclophosphamide, VCR, CPDD, and VP-16 resulted in transient tumor control in nearly 50% of infants with ependymoma. In this study, radiation was given after the completion of chemotherapy.²¹⁴ Attempts to use high-dose chemotherapy with agents like thiotepa, carboplatin, VP-16, and busulfan have not been effective in the setting of recurrence or in patients with newly diagnosed disease.

The outcomes of infants with several rare malignant primary CNS tumors, such as atypical teratoid/rhabdoid tumors (AT/RTs) and medulloepitheliomas, are quite poor, and the infants rarely survive. Although a variety of chemotherapeutic agents, some administered in high doses, have been used for children with atypical teratoid tumors, no chemotherapeutic regimen alone has yet demonstrated a response rate of more than 10 to 20% or the ability to induce long-term disease control. Older children with AT/RT treated with craniospinal and local radiotherapy and adjuvant chemotherapy have an apparent survival rate of more than 50% at 3 years.²¹⁵

The treatment of infants with low-grade tumors, especially low-grade gliomas, has been extensively evaluated over the past two decades. Increasing information suggests that chemotherapy, as outlined in the section on low-grade gliomas, will at least delay the need for alternative means of treatment for years after the initial diagnosis. However, infants with low-grade gliomas have a shorter period of EFS than do those older than 2 or 3 years at the time of treatment.

50.7 Conclusion

Given the uncertainty surrounding the “best” treatment for childhood brain tumors, chemotherapy should usually be used as part of a prospective treatment trial.

Pearls

- Chemotherapy has a definite role in the treatment of newly diagnosed medulloblastoma.
- Chemotherapy may result in objective tumor shrinkage in childhood low-grade gliomas and delay the need for radiotherapy.
- Chemotherapy can delay and in some cases obviate the need for radiotherapy in infants and young children with malignant brain tumors, primarily those with localized disease who have minimal residual disease after surgery.
- Chemotherapy is often a significant component of the multidisciplinary management of children with brain tumors.
- Molecularly targeted therapy is being actively explored in children with brain tumors, but these agents have not yet been incorporated effectively into treatment approaches.

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51 Radiotherapy of Pediatric Brain Tumors

Thomas E. Merchant and Erin S. Murphy

During the past 20 years, the role of radiation therapy in the treatment of childhood brain tumors has increased owing to the promise of new treatment methods and an improved understanding of the indications, critical parameters, and side effects attributed to this modality. Future investigations will tailor the selective use, sequencing, and escalation and de-escalation of radiation dose and volume. Advancement beyond conformal and intensity-modulated radiation therapy is anticipated with the use of proton therapy. The latter has been used only in its earliest form (passively scattered or three-dimensional conformal proton therapy) and will soon give way to the preferred method of spot scanning, which will allow intensity-modulated proton therapy.

51.1 Medulloblastoma

Medulloblastoma is the most common malignant brain tumor in children and presents at a median age of 5 to 7 years. The negative consequences of this tumor and the side effects of irradiation are offset only by the knowledge that radiation therapy has curative potential, in even the most advanced cases.

51.1.1 Prognostic Factors

Prognostic factors for medulloblastoma include the extent of disease and resection, age at presentation, and the intensity and quality of radiation therapy and chemotherapy. The effect of age at presentation is highly correlated with the selection of treatment and the delay or omission of radiation therapy in the front-line management of the disease in very young children. More recently, histopathologic and molecular subtyping studies have identified small subgroups for which survival is excellent or very poor.¹⁻⁴ How the histopathologic and molecular grouping affects the use of radiation therapy remains to be determined.

51.1.2 Radiotherapy

Several decades ago, the standard of care for children with medulloblastoma included surgery and craniospinal irradiation; chemotherapy was experimental. Craniospinal irradiation included treatment of the neuraxis, including all subarachnoid volumes contiguous with the central nervous system (CNS) and cerebrospinal fluid (CSF) pathways, and supplemental ("boost") irradiation of the primary site. The neuraxis component of therapy received 36 Gy, and the boost volume, formerly the anatomical posterior fossa, received approximately 54 Gy.

Treatment of Standard-Risk Medulloblastoma

The use of craniospinal irradiation changed markedly when investigators explored reducing the craniospinal dose for patients characterized as having standard-risk disease (i.e., those without metastatic disease or substantial residual or extensive tumor). In 1999, the Children's Cancer Group CCG-9892 study

showed that the addition of postradiation chemotherapy (lomustine, vincristine, and cisplatin) to a reduced-dose (23.4 Gy) craniospinal irradiation regimen resulted in a 5-year progression free survival (PFS) of 79%; thus, the addition of chemotherapy to the treatment regimen permitted a 12.6-Gy reduction in the craniospinal dose without affecting the rate of tumor progression.⁵ Since then, little has changed therapeutically in terms of disease control. Indeed, the confirmatory A9961 study (conducted between 1996 and 2000 and reported in 2006) showed that a postradiation regimen of vincristine, cisplatin, and lomustine resulted in a 5-year event-free survival (EFS) rate of 82%; the combination of vincristine, cisplatin, and cyclophosphamide resulted in a rate of 80%.⁶ The latter regimen had a slightly higher rate of acute toxicity, and some concern remains about the high incidence of secondary tumors in this treatment group.

Complications

The classic portals for the boost volume included a pair of parallel opposed beams targeting the entire posterior fossa with margin. When this type of treatment was delivered to very young children, the loss of IQ was approximately 4.2 points per year, even at the reduced craniospinal dose of 23.4 Gy.⁷ Children who likely started out with a low-average IQ would be expected to have a subnormal IQ within 3 years after completing radiation therapy. With no plateau, intellectual disability would be expected by 5 to 6 years after treatment. It was concluded that unless the method of primary site irradiation (posterior fossa boost) was modified, very little could be done to change the volume receiving the highest (> 45 Gy) doses.

The first prospective trial to reduce the dose to the posterior fossa was conducted between 1996 and 2003 in children with standard-risk medulloblastoma, defined as T1 to T3B and M0 disease according to the Chang staging system.⁸ Postoperative residual disease measuring less than 1.5 cm² received craniospinal irradiation (23.4 Gy), conformal posterior fossa irradiation (36 Gy), and conformal primary site irradiation (55.8 Gy) with a 2-cm clinical target volume margin. Radiation therapy was followed by high-dose chemotherapy with peripheral blood stem cell support. Children treated with this regimen, which reduced the volume of the posterior fossa receiving the prescribed boost dose by almost 15%, had a 5-year EFS rate of 83.0% (standard deviation [SD], 5.3%), and no change was noted in the pattern of treatment failure. This modest reduction in the volume receiving the highest dose lowered IQ loss to only 2.4 points per year.⁹

Emerging data strengthen the association between the distribution of dose to regional volumes of normal brain and decline in cognitive function in several domains. The negative effect on IQ and academic test scores associated with increasing mean dose was shown for the entire brain volume, supratentorial brain volume, left and right temporal lobes, and left hippocampus (IQ, math and reading scores).¹⁰ Proton therapy is an excellent measure to reduce extra-CNS and CNS doses in these patients: photon dose volume data associated with a decline in IQ are graphically inferior to proton dose volume data for similar patients.¹¹

Another important and devastating side effect of radiation therapy is CNS necrosis. Among 148 patients who received 23.4 Gy of craniospinal irradiation and 88 patients who received more than 36 Gy of craniospinal irradiation, the cumulative incidence of CNS necrosis at 5 years was 3.7% (SD, 1.3%).¹² Those patients in whom CNS necrosis was observed had the largest infratentorial volumes, receiving doses in excess of 50, 52, and 54 Gy, providing new limits of tolerance for children with medulloblastoma and other CNS embryonal tumors treated with aggressive surgery, craniospinal irradiation, and intensive chemotherapy.

51.1.3 Treatment Alternatives

Biology is likely to have an effect on risk stratification in future trials. Because 30% of patients present with metastatic disease, extent of disease will remain an important factor. By histopathology, 10% of patients have desmoplastic medulloblastoma and a favorable prognosis, 74% have classic medulloblastoma and an intermediate prognosis, and 16% have anaplastic medulloblastoma and a poor prognosis. According to the biological subgroup classification, 13% of patients have Wnt pathway activation and an excellent prognosis, 17% have sonic hedgehog activation and a less favorable outcome, and the remaining 70% have biological tumor subtypes and a range of outcomes ranging from average to poor. Options for managing patients who have standard-risk disease with favorable clinical–pathologic and molecular risk features include omitting radiation therapy altogether, omitting craniospinal irradiation, and reducing the dose to the neuraxis and primary site. For patients with high-risk disease, considerations include intensifying the radiation dose and volume, administering chemotherapy and radiation therapy concurrently, and escalating the dose at the primary site if local treatment failure is the associated pattern of failure.

51.1.4 Medulloblastoma in Patients Younger than 3 Years

Some of the greatest recent changes in how medulloblastoma is treated have been in the youngest patients. More recent studies have used radiation therapy in the front-line management of these patients following an approximately 4-month-long induction phase of postoperative chemotherapy. The Pediatric Brain Tumor Consortium PBTC-001 study reported in 2005 used the standard four agents of cisplatin, vincristine, cyclophosphamide, and etoposide, in conjunction with intrathecal mafosfamide, followed by radiation therapy.¹³ Radiation therapy was risk-stratified on the basis of age and extent of disease and ranged from 45 Gy (cumulative primary site dose) for the younger and lowest-risk group (after gross total resection) to 54 Gy for the older patients and those with residual disease at the time of irradiation. The 5-year PFS rate exceeded 50% in the cohort of children in whom craniospinal irradiation was omitted.

In the Children's Oncology Group (COG) A9934 study, the use of similar systemic chemotherapy without intrathecal therapy and focal irradiation to 50.4–54 Gy resulted in a 4-year PFS rate of 50% (SD, 6%).¹⁴ PFS rates were improved by using a strategy of initial surgery; induction chemotherapy for 4 months; second surgery when necessary; and age-, risk-, and response-adaptive conformal radiation therapy with posterior fossa treatment and

primary site irradiation, followed by 8 months of chemotherapy with conventional agents. The A9934 study included irradiation with a 10-mm clinical target volume margin. Patients whose disease progressed during induction chemotherapy experienced primary site treatment failure, whereas those with disease progression after radiation therapy experienced neuraxis failure in the spine or regions of the brain that were spared by the omission of craniospinal irradiation (► Fig. 51.1). The newer regimens that prescribe early but not immediate postoperative radiation therapy have a very high rate of local tumor control.

51.1.5 Reducing Radiation Dose and Volume

As outlined earlier, clinical–pathologic and molecular risk classification will help to stratify patients for treatment. Radiation dose and volume may be able to be reduced in some children with medulloblastoma. Strategies for achieving such reductions include reducing the craniospinal dose to 18 Gy, as was done in the COG ACNS0331 trial; reducing the cumulative dose to the primary site to 45–50 Gy, as was done in the PBTC-001 and A9934 trials; and reducing the clinical target volumes for the boost component of therapy. Other strategies to consider are partial irradiation of the tumor bed and radiation therapy methods that spare normal tissue, such as intensity-modulated photon therapy or one of the current or developing methods of proton therapy.

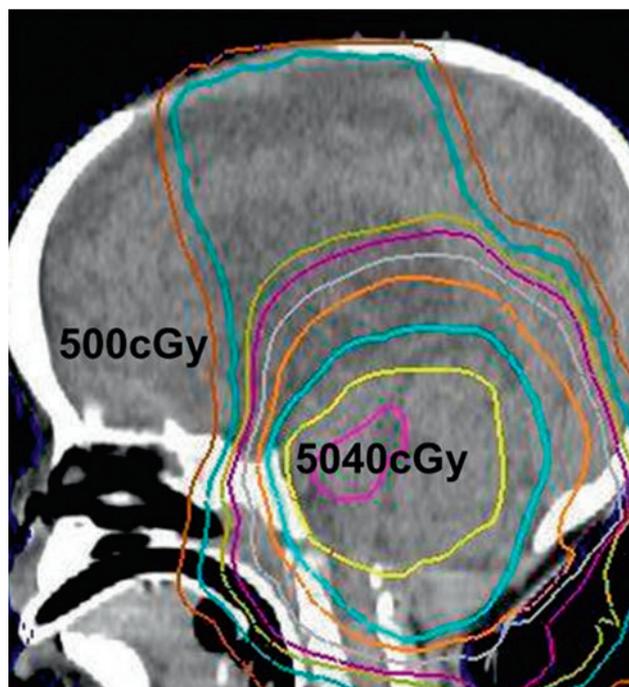


Fig. 51.1 Sagittal computed tomographic scan of a very young child (age younger than 3 years) with medulloblastoma treated in the Children's Oncology Group A9934 study by conformal radiation therapy (ca. 2000). Dose gradient from 5,040 to 500 cGy is apparent. Low-dose regions were the site of metastatic failure after radiation therapy.

51.2 Ependymoma

Ependymoma is the third most common brain tumor in children. The incidence is highest in very young children, which is relevant when the indications for radiation therapy are considered. In children, ependymoma most often arises in the infratentorial compartment and is intimately associated with neurovascular structures and the brainstem. This is important because of the normal tissue dose constraints that one must consider in planning radiation therapy. Supratentorial ependymoma may arise in the lining of the ventricular system or within brain parenchyma. In these cases, the postoperative tumor bed may range from a simple spherical structure to a large intracranial cavity, with associated subdural hygroma or complex or unidentifiable tumor volume.

51.2.1 Three-Dimensional Radiation Therapy

In 1993, the International Commission on Radiation Units and Measurements outlined a nomenclature for target volumes and three-dimensional radiation therapy planning. These recommendations were first adopted for the treatment of ependymoma in the St. Jude Children's Research Hospital RT1 trial. The gross tumor volume was defined as the residual tumor and/or the tumor bed; the clinical target volume was an expansion of the gross tumor volume, with an additional margin of 10 mm that was anatomically constrained at barriers where tumor invasion was unlikely (e.g., base of skull, calvaria, tentorium); and the planning target volume (PTV) was a margin meant to account for geometric uncertainty (3 to 5 mm). The trial included 153 patients treated between 1997 and 2007. The 7-year EFS and overall survival (OS) rates were 72% (SD, 6%) and 81% (SD, 5%), respectively. The 7-year local control rate was 83% (SD, 5%), the 7-year cumulative incidence of local failure was 16.3% (SD, 3.4%), and the 7-year cumulative incidence of distant metastasis was 11.5% (SD, 2.9%).¹⁵

51.2.2 Reducing Radiation Volume

The initial experience with three-dimensional planning for ependymoma included multiple beams at various orientations pointed at the planning target volume. Each beam had the beam's eye view shape of the planning target volume. The intersection of the beams results in a dose distribution that is adjusted and weighted to shape the prescribed dose (54 to 59.4 Gy) to the planning target volume. When treatment plans were initially developed with this early three-dimensional treatment-planning process, it was apparent that large volumes of normal brain could be spared in the process of treatment planning and delivery.

These methods were further refined to include intensity-modulated radiation therapy, a more sophisticated form of three-dimensional conformal radiation therapy in which computation-intensive iterative planning is used to balance dose constraints for normal tissues against target volume coverage goals. The prospect of sparing normal tissues in a young and vulnerable patient population accelerated referrals for systematic conformal radiation therapy in the late 1990s and likely led to the more aggressive preradiation optimization of patients to minimize the amount of residual disease before irradiation. A targeting example for ACNS0831, the current COG trial, appears in ► Fig. 51.2.

51.2.3 Complications

Cognitive outcomes were reported along with disease control for the patients with ependymoma in the St. Jude Children's Research Hospital RT1 trial.¹⁶ No decline in IQ was noted for the entire group, including the cohort of younger children (age younger than 3 years). The latter group had lower baseline values and no decline with time. With additional follow-up, now extending to more than 10 years, evidence that conformal radiation therapy spares cognition remains apparent. As an example, no clinically significant declines occur in the academic achievement of children with ependymoma treated with conformal radiation therapy.¹⁷ Similarly, verbal and visual auditory learning¹⁸ and adaptive behavior¹⁹ appear to be spared in children with ependymoma treated with focal conformal radiation therapy.

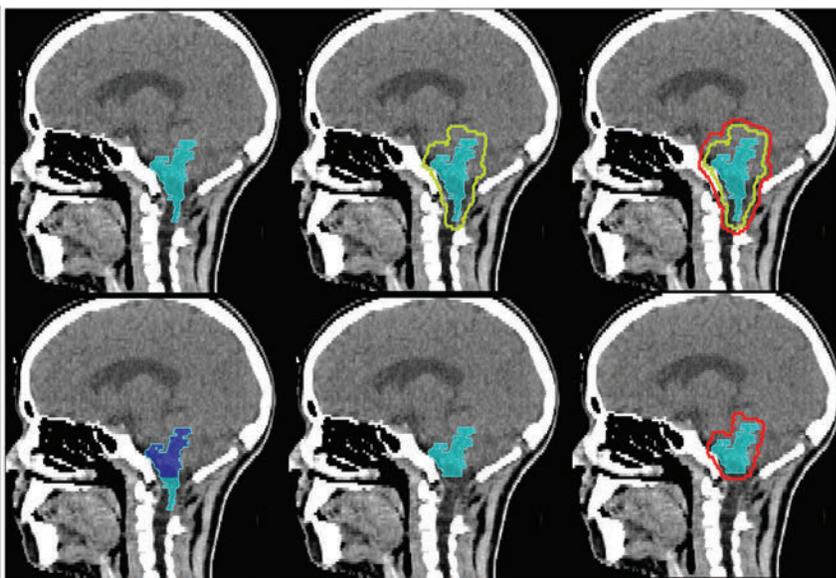


Fig. 51.2 Sagittal computed tomographic scans of a child with infratentorial ependymoma after gross total resection targeted for radiation therapy according to the ACNS0831 Children's Oncology Group guidelines. The postoperative tumor bed defines the gross tumor volume (upper, left), surrounded by a 5-mm anatomically constrained clinical target volume margin (upper, center) and a geometrically expanded 3-mm planning target volume margin (upper, right) targeted to receive 5,400 cGy. The second phase of treatment, an additional 540 cGy, targets the gross tumor volume, excluding the portion that is adjacent to the upper cervical spinal cord (lower, left and center). The modified gross tumor volume is geometrically expanded by 3 mm to create a second planning target volume (lower, right).

One of the added benefits of conformal radiation therapy is the ability to associate more precise estimates of radiation dose with functional outcomes. The dose to the hypothalamus has been directly correlated with the incidence and time to onset of clinically significant endocrine deficiencies in children with ependymoma and other brain tumors. Growth hormone secretion is the most common endocrine deficiency and the most sensitive to radiation dose.

Neurologic effects of irradiation on motor and sensory function and coordination are rare and are most often associated with infrequent cases of radiation necrosis. However, the effect of irradiation on recovery from tumor-related and surgery-acquired deficits should be considered, especially in children with infratentorial ependymoma after surgery for locally extensive disease. Prospective data suggest that the radiation dose does not impede recovery of neurologic function in children with ependymoma.

One additional aspect of neurologic function to consider is hearing loss after radiation therapy. Hearing loss as a function of time after radiation therapy is relatively uncommon, especially when the total dose to the cochlea can be limited to 45 Gy.²⁰ Thus, preservation of hearing is largely achievable in most patients when the target volume margins and parameters of some of the aforementioned clinical trials are used. With smaller clinical target volume margins, more precise methods of localization and verification, and intensity-modulated radiation therapy or proton therapy, irradiation of the cochlea with doses that will result in hearing loss should be infrequent unless the internal auditory canal is part of the intracranial volume at risk.

51.3 Low-Grade Glioma

Low-grade gliomas make up approximately 26% of childhood CNS malignancies seen in the United States.²¹ Low-grade gliomas are a heterogeneous group of tumors that are located most commonly in the cerebellum, followed by the cerebral hemispheres, the deep midline structures, the visual pathways, and the brainstem. Observation after gross total resection is the standard of care and can produce PFS rates of 80% for grade II tumors and more than 90% for grade I tumors.²² Tumors may demonstrate an indolent natural history after incomplete resection, but the PFS rate at 5 years is only 55%.²³ Therefore, neurologic symptoms, progression on imaging, or risk for progression at a critical site necessitates treatment with either radiation or chemotherapy. The choice of treatment remains controversial, particularly for younger children.

51.3.1 Treatment Alternatives

The sequencing of therapy is affected by physician bias, patient age, tumor location and grade, risks associated with progression, severity of symptoms, and lack of randomized evidence. Some studies show that immediate adjuvant radiotherapy improves PFS rates,^{24–26} and one study suggests that such treatment improves seizure control.²⁴ Adjuvant radiotherapy after incomplete surgical resection increases the 10-year PFS rate from 40 to 82%.²⁶ More controversial is the benefit of immediate radiotherapy on survival in this setting, with only one study showing that immediate radiotherapy offers a survival benefit.²⁷ A trend toward survival benefit for radiotherapy has

also been shown for World Health Organization (WHO) grade II tumors.²⁸ However, the majority of studies demonstrate no survival advantage with the addition of radiotherapy.^{24,26,29,30} Therefore, after an incomplete resection, a course of observation is usually recommended for asymptomatic patients who are not at severe risk for neurologic compromise if the tumor progresses. The addition of radiotherapy to chemotherapy has demonstrated a PFS benefit over chemotherapy alone³¹; however, the ideal timing and sequence of radiotherapy and chemotherapy remain unknown.

51.3.2 Three-Dimensional Conformal Radiotherapy

Radiotherapy techniques have improved over time. A Phase II trial of three-dimensional conformal radiotherapy resulted in excellent 10-year EFS and OS rates of 74% and 96%, respectively.³² The tumor volumes were based on magnetic resonance images, and a 1-cm clinical target volume margin was used. Among 78 patients, 13 developed treatment failure: 4 with metastatic progression, 1 with marginal failure, and 8 with in-field failure. All patients were prospectively evaluated to determine the effect of conformal radiotherapy on cognitive abilities, hearing, and endocrinopathies.³³ It is important to note that patients with more aggressive surgery up front or with neurofibromatosis type 1 and younger children had lower baseline neurocognitive function before radiotherapy. Also, 24% of tested patients had growth hormone abnormalities before the initiation of radiotherapy. Cognitive effects 5 years after conformal radiotherapy correlated with patient age, neurofibromatosis type 1 status, tumor location and volume, extent of resection, and radiation dose. The effect of age exceeded that of radiation dose, and patients younger than 5 years experienced the greatest decline in cognition.

51.4 Optic Pathway Tumors

Radiation therapy is highly effective for optic pathway tumors, with 10-year PFS rates higher than 80%.^{34–37} The initial choice of therapy does not affect survival, but when radiotherapy is administered, PFS rates at both 5 and 10 years are improved.^{22,34,38} Many patients with optic pathway tumors present at a young age, with 25% younger than 18 months and 50% younger than 5 years.^{39,40} For children younger than 2 years, younger age and diencephalic syndrome are poor prognostic factors.⁴¹ After combination chemotherapy, progression has been noted at a median of 3 years from treatment.⁴² At the time of progression, second-line chemotherapy, surgical resection, and radiation therapy need to be considered, with a decision made by a multidisciplinary team. Data suggest that patients who undergo surgery before radiation therapy enter treatment with better visual acuity and have better long-term outcomes⁴³ (► Fig. 51.3).

51.5 World Health Organization Grade I Tumors

WHO grade I astrocytomas include juvenile pilocytic astrocytoma and subependymal giant cell astrocytoma and are generally characterized by well-circumscribed lesions.⁴⁴ Juvenile pilocytic astrocytomas are most commonly in the cerebellum

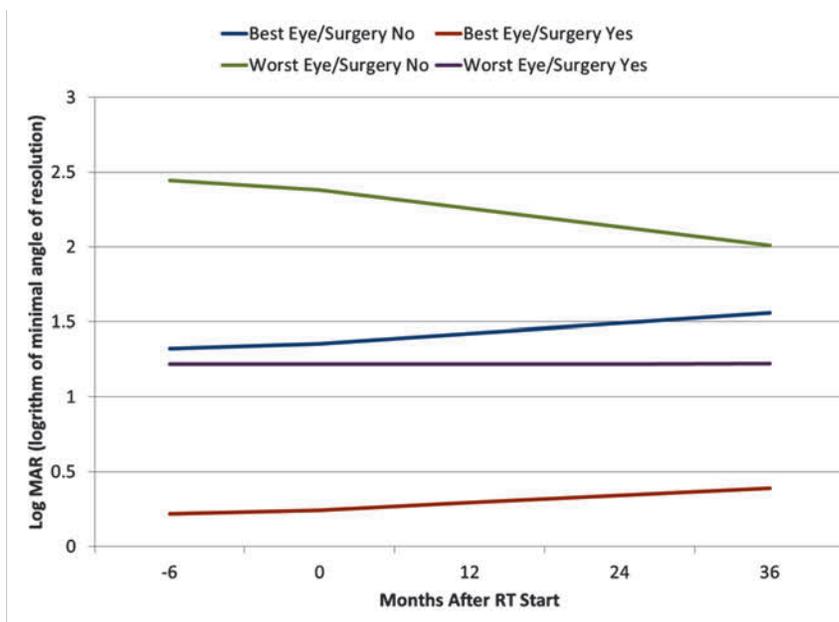


Fig. 51.3 Visual acuity before and after radiation therapy based on eye condition and surgical intervention. Log MAR 0 = 20/20; log MAR 1 = 20/200. Log MAR, logarithm of minimal angle of resolution. (Source: Awdeh RM, Kiehna EN, Drewry RD, et al. Visual outcomes in pediatric optic pathway glioma after conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;84 (1):46–51.⁴³)

and the diencephalic region; only 3% of patients have disseminated disease. Subependymal giant cell astrocytomas develop along the lining of the ventricles and are associated with tuberous sclerosis.

The primary treatment for WHO grade I tumors is maximal safe resection. The 15-year survival rate for completely resected tumors is 90%.⁴⁵ Radiation is recommended for symptomatic or progressive disease that cannot be resected or for residual disease with the potential to grow and damage critical structures.

Infratentorial tumors are more likely to be resectable,³⁵ whereas tumors in the deep tissues of the brain are less likely to be completely resected; therefore, they are likely to benefit from radiotherapy.⁴⁵ Children with deep-seated tumors treated with surgery and radiotherapy have a 15-year survival rate of 64%.⁴⁵ The recently changed WHO criteria now classify ganglioglioma as a WHO grade I tumor. These tumors do not respond as well to irradiation or chemotherapy as their pilocytic counterparts do.

51.6 World Health Organization Grade II Tumors

WHO grade II gliomas include diffuse astrocytoma, pleomorphic xanthoastrocytoma, oligodendroglioma, oligoastrocytoma, and pilomyxoid astrocytoma.⁴⁴ These tumors are more likely to progress than are WHO grade I tumors. A report of 90 children with WHO grade II glioma describes 5-year OS and PFS rates of 90% and 56%, respectively, with 10-year rates of 81% and 42%, respectively.³⁹ Of note, for patients older than 3 years without a gross total resection, the early administration of radiation does not appear to influence PFS or OS rates: the 10-year PFS rate is 43% whether the patients receive radiotherapy early or at the time of progression. A 15-year cumulative incidence of malignant transformation of 6.7% has been reported from a group of patients with low-grade (grade II) gliomas and did not correlate with the use of radiotherapy.⁴⁶

51.7 High-Grade Glioma

High-grade gliomas, including anaplastic astrocytoma (WHO grade III), anaplastic oligodendroglioma (WHO grade III), and glioblastoma multiforme (WHO grade IV), comprise 10 to 20% of pediatric brain tumors. These tumors are most commonly found in the cerebral hemispheres, thalamus, or basal ganglia. The molecular profile of childhood high-grade glioma is different from that of adult high-grade glioma and more often resembles that of a secondary glioblastoma multiforme, with an abundance of *TP53* mutations. Standard treatment for these aggressive tumors includes maximum safe resection followed by radiotherapy and chemotherapy, given either concurrently or sequentially. Gross total resection (i.e., >90% tumor resection) confers a clear PFS benefit.^{47–49} The most recent clinical trial reported 3-year EFS and OS rates of 11% ± 3% and 22% ± 5%, respectively, for a treatment regimen that included the administration of temozolomide concurrently with and after irradiation.⁵⁰ These results were inferior to those from a prior series⁴⁷ that included radiation therapy followed by multiagent chemotherapy. The respective 3-year and 5-year OS rates are 35% and 36% when children receive multimodality therapy.^{47,51} However, patients in a Phase II trial did not benefit from high-dose chemotherapy given before radiotherapy.⁵¹

51.8 Brainstem Glioma

The term *brainstem glioma* refers to both focal (20%) and diffuse intrinsic (80%) tumors.⁵² Patients with diffuse intrinsic tumors typically have a dismal prognosis, with a median OS of no more than 12 months.^{52–57} A short duration of presenting symptoms correlates with a worse survival.^{58,59} Attempts to improve outcomes have included hyperfractionated radiotherapy with total doses ranging from 66 to 78 Gy, resulting in median survival times of 8 to 13 months.^{60–67} A French trial reported improved survival of 17 months when front-line chemotherapy was used

before radiotherapy; however, the chemotherapy caused significant infections and increased hospitalization.⁶⁸ Concurrent chemotherapy has not demonstrated a benefit,^{63,69,70} nor have other strategies, including selective blood-brain barrier disruptors combined with chemotherapy,⁷¹ concurrent inhaled carbogen,⁵⁴ intravenous recombinant interferon- β ,⁷² and adjuvant chemotherapy.⁷³

51.9 Germ Cell Tumors

Pure germinomas, nongerminomatous germ cell tumor (NGGCT) subtypes (i.e., embryonal carcinoma, endodermal sinus tumor, choriocarcinoma), and teratomas comprise up to 70%, 20%, and 20% of all germ cell tumors, respectively. Together, these tumors account for approximately 4% of pediatric CNS neoplasms.^{32,74} They typically arise in the midline of the third ventricle, most commonly posteriorly in the pineal region, or by the anterior recess of the third ventricle.⁷⁵

51.9.1 Treatment Alternatives

Treatment for germ cell tumors continues to evolve over time and is based on the tumor type. Before safe biopsy of these tumors became available, radiotherapy was used as a diagnostic tool. If a tumor demonstrated a quick response to a radiation dose of 20 Gy, then it was classified as a germinoma.^{76,77} Now, stereotactic biopsy is often used to obtain a diagnosis and has a reported mortality rate of 1.3% and a neurologic morbidity rate of 3%.⁷⁸ Radical resection offers no benefit over biopsy alone for intracranial germinoma.⁷⁹ However, there is a benefit to surgical resection for NGGCT, in the form of both more accurate diagnosis⁷⁴ and better overall outcomes,⁸⁰ when it is combined with chemotherapy and radiation.

Radiation therapy is curative for pure germinoma, with reports documenting 10-year cause-specific survival and OS rates of up to 100% and 83%, respectively, for pathologically verified germinoma.^{77,81,82} A single-institution experience demonstrated 5-year rates of spinal axis failure and intracranial failure of 49% and 45%, respectively, for patients treated with partial-brain radiotherapy, compared with rates of 0% and 6% for those receiving whole-brain radiotherapy or craniospinal irradiation.⁸² The addition of chemotherapy has allowed volume and radiation dose to be reduced with equally good results.^{83–85} Prospective trials from the Société Internationale d'Oncologie Pédiatrique (French Society of Pediatric Oncology) and the Japanese Study Group show that relapses occur within the ventricles when involved-field radiotherapy (IFRT) is used after chemotherapy and have now changed their radiotherapy target to whole-ventricle irradiation (WVI) following chemotherapy.^{86–88}

Survival rates of patients with NGGCTs treated with chemotherapy followed by craniospinal irradiation with a boost to the primary site range from 67 to 74%.^{80,89} A Phase II COG trial for NGGCTs (ACNS0122) investigated neoadjuvant chemotherapy followed by 36 Gy of craniospinal irradiation and a boost to the primary tumor site or resection cavity for a total dose of 54 Gy. The patients who experienced a complete or partial response at the end of induction or who had mature teratoma or fibrosis at the time of second-look surgery had excellent 3-year EFS rates

ranging from 85.7 to 94.1%.⁹⁰ Therefore, ACNS1123 is investigating the role of reduced-volume radiotherapy (30.6 Gy of WVI and 54 Gy of IFRT) for patients with a good prognosis. The Japanese Study Group has reported outcomes of the treatment of patients with an intermediate prognosis with five cycles of carboplatin and etoposide, followed by WVI to 30.6 Gy and IFRT to 50 Gy, with 10-year PFS and OS rates of 81.5% and 89.3%, respectively.⁸⁸

51.10 Craniopharyngioma

Although craniopharyngioma in children is a histologically benign tumor, management with surgery and radiotherapy may be associated with varying morbidity. Complications include neurologic deficits, panhypopituitarism, diabetes insipidus, cognitive deficiencies, behavioral problems, visual disturbances, vasculopathy, malignant transformation, and secondary malignancies.^{91–97} Great care should be taken when therapeutic decisions are made for these children.

Craniopharyngioma can be managed with a gross total resection alone; however, even when gross total resection is confirmed by neuroimaging, the rate of recurrence is from 20 to 27%.^{98,99} Recurrence after surgery is related to tumor size, residual calcifications detected by computed tomography, and history of prior surgery or irradiation.^{98,99} The alternative to radical surgery is limited surgery and focal irradiation. The St. Jude Children's Research Hospital experience suggests that fewer complications occur after a combined-modality approach and a minimal extent of surgery have been used.¹⁰⁰ Ten-year PFS rates from 84 to 100% have been reported when patients undergo limited surgical resection followed by radiotherapy.^{101–103} In pediatric patients with craniopharyngioma, several factors are significantly associated with worse neurocognitive outcomes: age younger than 7.4 years, more extensive surgery, multiple surgical procedures, diabetes insipidus, hydrocephalus, CSF shunt, shunt revisions, Ommaya reservoir laterality, and cyst aspirations.¹⁰⁴ IQ is also affected by radiation dosimetry factors, including percent volume of total brain, supratentorial brain, and left temporal lobe receiving doses greater than 45 Gy.

Radiation oncologists should be aware that tumor cyst expansion during treatment is common and that serial magnetic resonance imaging should be performed, with consideration given to developing a new plan when there is a risk for target volume compromise.¹⁰⁵ Similarly, consideration may be given to cyst aspiration or decompression during radiotherapy without delaying radiation treatments. ▶ Fig. 51.4 displays modeled IQ data after surgery and radiation therapy for craniopharyngioma, with the effects of age and diabetes insipidus (a marker of the extent of surgery) shown.

Stereotactic radiosurgery may be appropriate for patients with craniopharyngioma who have recurrent disease after prior fractionated radiotherapy or residual disease after surgical decompression. Important considerations for radiosurgery include tumor location, marginal tumor dose, dose tolerance of critical structures, and prior therapy.^{106–112} A single-institution report describes a 5-year local control rate of 68% for residual or recurrent craniopharyngioma treated with the standard marginal dose of 13 Gy.¹¹³

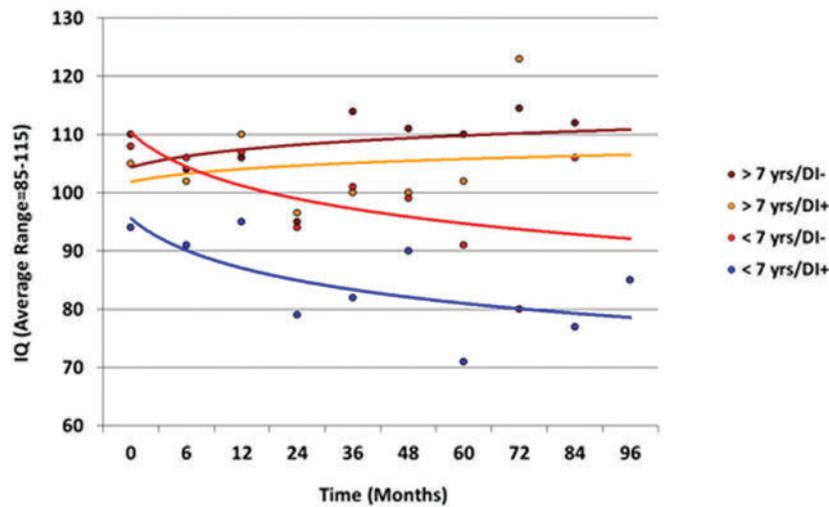


Fig. 51.4 IQ modeled as a function of time after irradiation, age, and diabetes insipidus. DI, diabetes insipidus.

Pearls

Patient Selection

- Radiation therapy is a component of front-line therapy in the management of nearly all childhood brain tumors.
- Be aware of current guidelines for target volume definition and associated treatment margins to minimize radiation dose and volume.

Surgical Optimization

- A greater extent of resection is associated with improved outcome in children with medulloblastoma, ependymoma, and high-grade glioma.
- There is no association between extent of resection and outcome in children with low-grade glioma, pure germinoma, and craniopharyngioma.

Sequencing and Response Assessment

- The early use of irradiation in the primary or adjuvant setting is associated with higher rates of control for most tumors.
- Pseudoprogression early after radiation therapy is common for many tumor types and does not indicate treatment failure.

Acute and Late Effects of Irradiation

- The side effects of radiation therapy have been reduced through the implementation of newer treatment methods.
- Tumor (hydrocephalus) and surgery-related morbidity contribute to the side effects observed after radiation therapy.
- There is a strong association between age at the time of irradiation and cognitive effects.

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Trauma

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52 Nonaccidental Head Injuries

Ann-Christine Duhaime

Few topics in pediatric neurosurgical practice engender so much controversy and elicit such strong opinions as does nonaccidental injury. It is an area that most surgeons wish they never had to encounter because it rarely involves surgery at all, and it often thrusts them into a medical and medicolegal maelstrom that many would prefer to avoid. Although neurosurgeons are practiced in making firm decisions with incomplete information on a daily basis, this arena is altogether different, and for many, it is both unfamiliar and uncomfortable territory. Yet because it is common, and because the opinion of the neurosurgeon often holds considerable weight, it is important to have an overall understanding of what is known and what is at present still unknown in this area. The purpose of this chapter is to provide a practical overview for the neurosurgeon called to manage a case in which the differential diagnosis includes inflicted injury.

52.1 History and Terminology

Because some of the confusion in the field of child abuse arises from semantics and terminology, it is useful to understand the background from which some of the labels used for various “syndromes” arose. That children might present with a complex of signs and symptoms resulting from mistreatment at the hands of their caretakers was widely recognized by the medical field only in the middle of the 20th century, although the French physician Ambroise Tardieu attempted to raise awareness of child maltreatment a century earlier.¹ What is challenging, and often handicapping, about the presentation of these particular patients is that the true history of illness is usually withheld. Thus, the clinician must rely on the recognition of patterns of findings to infer that injury has occurred, and that it may not be accidental in etiology.

C. Henry Kempe, a pediatrician and chairman of pediatrics at Children’s Hospital Colorado, Denver, and his colleagues pioneered in the recognition of abusive injury in the United States with their description of children who presented for a variety of reasons but had certain physical and behavioral characteristics in common, and whose symptoms and signs resulted from chronic physical abuse and neglect.² Their so-called “battered child syndrome” was the first widely promulgated clinical constellation to bring the problem of inflicted injury into the consciousness of general pediatrics.

Moving into the realm of even younger children, John Caffey, a pediatric radiologist at the Children’s Hospital of Pittsburgh, Pennsylvania, noticed the relationship between long-bone metaphyseal fractures, subdural hematomas, and retinal hemorrhages in infants. In the 1960s and early 1970s, the role of angular deceleration forces in the biomechanics of concussive head injury and subdural hematoma was being recognized in primate experiments and in some case reports of adult head injury.^{3–5} Another event that contributed to how this new syndrome was conceptualized involved a well-publicized case in England during the late 1940s and 1950s, in which a nursemaid confessed to apparently causing injury to a number of her charges by shaking them in order to burp them.⁶ Thus, it was surmised

that manual shaking could generate sufficient angular deceleration of the infant head to result in the subdural hemorrhages commonly seen in these infants, and that shaking was therefore the causative mechanism. Caffey coined the term *whiplash shaken infant syndrome* to denote this condition, which became known in common parlance as shaken baby syndrome.^{7,8} Central to Caffey’s concept was that shaking was widely perceived as a nonharmful and acceptable method of discipline for infants, and that caretakers were unwittingly causing highly damaging or fatal injuries to their children by this practice.⁶

The past two decades have seen increasing recognition that inflicted head injury can take many forms. Single acute neurologic events, acute or healing skeletal trauma, and chronic subdural hemorrhages alone or in combination, with or without retinal hemorrhages, bruising, or signs of physical neglect, may be seen. The common findings of apnea and hypoxia are suspected by many to contribute to the pathogenesis of the more severe end of the acute injury syndrome.⁹ Neuropathologic findings in the cervical spine have been recognized, and whether trauma in this region, caused by manual shaking or some other mechanism, contributes to the clinical picture is an area of ongoing investigation.^{10–12} However, because the vast majority of children with inflicted injury have subdural hematomas, hypoxia alone seems unlikely as a full explanation for all the findings. As in other branches of medicine, it has become clear that the relatively simple notions of mechanism and context initially proposed in the 1960s and 1970s provided a useful and practical starting point, but that much more work is needed before clinicians have available a full and generalizable understanding of these types of injuries. For this reason, many authors and child advocacy organizations have adopted terminology that does not imply a single mechanism of injury but instead is more general, if admittedly less riveting, than “shaken baby syndrome.”¹³

As a matter of definition, in this chapter the terms *inflicted injury*, *nonaccidental injury*, and *abusive head injury* are used interchangeably to refer to trauma resulting from the deliberate application of force to a child.

52.2 Epidemiology

Research in the epidemiology of inflicted trauma has been hampered by the same factors inherent in research into other aspects of this topic, including difficulties with ascertainment, inclusion criteria, and follow-up. Nonetheless, several population-based studies have been conducted, and these serve to estimate the incidence of inflicted neurotrauma. A prospective population-based study in Scotland found that “shaken impact syndrome” occurred with an annual incidence of 24.6 per 100,000 children younger than 1 year of age. Cases were more common in urban areas and during autumn and winter. The risk for sustaining an inflicted head injury by 1 year of age was found to be 1 in 4,065.¹⁴ At least 24% of children younger than 2 years of age admitted to the hospital for head injury have sustained nonaccidental trauma.¹⁵

Inflicted neurotrauma is a syndrome of young children, with a mean age younger than 1 year.¹⁶ In most studies, boys are slightly more at risk than girls, although some studies show equal incidence rates.

Risk factors for inflicted injury include young parents, low socioeconomic status, socially unstable households, single parents, prematurity of the infant, history of prior abuse to the caretaker, and psychiatric or substance abuse histories.^{17–21} Perpetrators in order of frequency include fathers (37%), boyfriends (20.5%), female babysitters (17.3%), and mothers (12.6%).²² In a significant percentage of cases, evidence of prior trauma is present or inferred, although single events are also common.^{23–25}

52.3 Clinical Presentation and History

The two most common histories given by caretakers when children present with nonaccidental head injury include a history of trivial blunt trauma and no history of trauma. When a history of trauma is obtained, it is most often one of a low-height fall, usually from a bed or other low surface.^{16,24,26–28} When children present without a history pointing to trauma, they are brought to attention because of specific symptoms or signs, including feeding difficulty or vomiting, lethargy, irritability, abnormal movements, seizures, apnea, and unresponsiveness. Occasionally, the diagnosis will be suspected on the basis of findings noted on routine physical examination, such as an enlarging head or unusual or patterned bruising. When no history of trauma is given and the symptoms are nonspecific, a diagnosis of inflicted injury often may be missed. In one study of 173 children with abusive head injury, it was ascertained that signs and symptoms of inflicted injury had been present, but the diagnosis missed, at prior presentations for medical care in nearly one-third of children.²³ The diagnosis was more likely to be missed in young, Caucasian children from intact families who did not present with respiratory compromise or seizures. In 4 of 54 missed cases, the later presentation resulted in a fatality, underscoring the importance of considering the diagnosis of inflicted injury even when symptoms are nonspecific and no history of trauma is provided. Other authors also have discerned racial differences in the evaluation obtained for children presenting for care with similar injuries, reinforcing the fact that ascertainment bias may contribute to missed injuries (or, conversely, to unnecessary testing).²⁹

The best and most helpful history is that obtained at the initial contact. The neurosurgeon should make it clear that the goal is to understand what happened to the child, in order to anticipate what kinds of injuries may have been incurred, to tailor evaluation and management, and to anticipate potential delayed complications. This is true for all head injuries, accidental or otherwise.

After the initial history is provided by the caretaker, specific questions need to be asked and answers obtained. Exactly what happened? At what time did it occur? Who was there? How high was the fall/drop/trajectory? What kind of surface did the baby hit, and with what part of the body? What position was the baby in? Who saw it? If the incident was unwitnessed, who heard it or arrived at the scene? What did the baby look like and do? For how long? What happened next? It may be helpful

to describe that what you are trying to create is a “mental video” of the events surrounding the injury. An exact description of the events is invaluable and is best obtained right away. If the person who witnessed the injury is not present, that person should be interviewed as soon as possible.

Because the vast majority of low-height falls in childhood are well tolerated and result in minimal injury, the finding of more serious injuries from this purported mechanism is one of the more common reasons why suspicion of inflicted injury is raised in emergency department and primary care clinicians. This diagnostic criterion falls under the concept of injuries “inconsistent with” or “inadequately explained by” the reported mechanism. However, exactly what mechanism causes what injuries at what age is incompletely understood, although some progress in this area has been made in recent decades (see later section on mechanisms and types of injury). Nonetheless, few clinicians called upon to evaluate potentially injured children are fully knowledgeable regarding the available data in this area. Hence, in practice, the criteria for considering inflicted injury vary among clinicians and hospitals. For example, despite ample evidence to the contrary,^{30–32} many clinicians still believe that the presence of a skull fracture in an infant is inconsistent with a low-height fall. Epidural hematomas can result from low-height falls in infants, and although they can be serious or even life-threatening, they are only rarely due to inflicted injury.³³ Even when similarities in injury types are accounted for, the frequency with which referrals for evaluation for possible nonaccidental injury are made has been shown to be influenced by a number of factors, including the presence of two parents, the insurance status of the patient, and the race of the infant.^{23,29}

Retinal hemorrhages are reported in 65 to 95% of children with inflicted head injury, may be unilateral or bilateral, and are best seen with the use of mydriatics.^{26,34–36} The exact biomechanics or other conditions necessary to cause retinal hemorrhages are at present not well understood; they can be associated with normal vaginal delivery, coagulopathy, hypertension, accidental trauma, subarachnoid hemorrhage, subdural hemorrhage, papilledema, and some other uncommon conditions, including certain genetic disorders and rare cases of resuscitation.^{37–46} When accidental trauma is minor or mild, retinal hemorrhages are usually sparse and may be unilateral.^{15,44,47} However, severe, bilateral retinal hemorrhages, especially if associated with retinal folds or detachments, are associated with major traumatic forces in accidental trauma or with nonaccidental injuries, and they have not been reported from low-height falls.^{42,48–52}

Although some medical conditions can mimic certain aspects of acute and chronic inflicted injury, generally these conditions can be identified with a complete history and physical examination, appropriate imaging studies, and sometimes other specific evaluations, such as laboratory tests.^{43,53–55} Of somewhat greater difficulty is the distinction between inflicted and accidental trauma, and this will be discussed in more detail below. However, although there may be some diagnostic uncertainties in the assessment of possible nonaccidental trauma, there is no illness or condition known besides inflicted injury that causes the combination of acute subdural hemorrhage, healing skeletal injuries, and severe bilateral retinal hemorrhages (particularly if retinal folds or detachments are seen). When a single severe traumatic event (i.e., one involving very high-magnitude forces)

has occurred, acute subdural hemorrhage, acute fractures, and severe bilateral retinal hemorrhages may occur, but this combination of findings has not been reported in association with low-height falls.

52.4 Diagnostic Imaging

Nearly all types of head injury have been reported in the context of inflicted mechanisms, but the most common is acute subdural hematoma.^{12,15,16,35,56} Often, the hemorrhages are thin but extensive collections over the surface of one or both cerebral hemispheres, as well as in the posterior interhemispheric fissure (► Fig. 52.1). In some children, the brain parenchyma appears normal. In other children, parenchymal hypodensities may be present initially or appear within the first 1 to 2 days after trauma and may range from focal and patchy to extensive.^{57–59} In the latter case, an entire hemisphere or both supratentorial compartments may be affected, the so-called “big black brain”⁶⁰ (► Fig. 52.2). This extensive hypodensity does not appear in all children with inflicted injury but is seen in a subset of those who are the most impaired at presentation. The pathophysiology of this phenomenon is incompletely understood, but it seems to be unique to infants and young children. Diffuse hypodensity is bilateral in two-thirds of cases and unilateral in one-third, with the latter constellation more common in older infants and young children. Unilateral cases often include an affected region in the contralateral medial frontal region due to subfalcine herniation (► Fig. 52.2). In such cases, the

hypodensity is usually present on the side of the greater subdural hemorrhage.^{36,58,59,61,62} The observation that one-third of children with this finding have the unilateral form also argues against a pathophysiology related solely to apnea/hypoxia.⁶² Children in whom unilateral or bilateral “big black brain” develops usually are unresponsive on admission and have a mortality of 67%. Survivors tend to be very young, probably because the ability of the calvaria to expand serves as some protection against brainstem compression and fatal herniation.⁶¹ Outcome in survivors of bilateral hypodensity is dismal, with children remaining blind, nonverbal, nonambulatory, and profoundly developmentally impaired, thus making the utility of aggressive acute intervention in such cases arguable.⁶³

Magnetic resonance (MR) imaging may be helpful in identifying small subdural hemorrhages and parenchymal contusions that may be inapparent on a computed tomographic (CT) scan. However, the early hope that subdural hemorrhages could be reliably dated by MR imaging has not been realized because the multicompartmental nature of the traumatized subdural and subarachnoid spaces makes hemorrhagic collections layer and mix in various ways that may influence their signal characteristics.^{64,65} Thus, the dating of hemorrhages is only approximate and is not generally accurate to within specific hours or days, as is sometimes needed in criminal investigation. Diffusion-weighted imaging and spectroscopy have been used to corroborate the degree of parenchymal injury seen on CT.^{66,67} One of the main practical values of MR imaging is that it distinguishes extra-axial cerebrospinal fluid collections from hemorrhagic

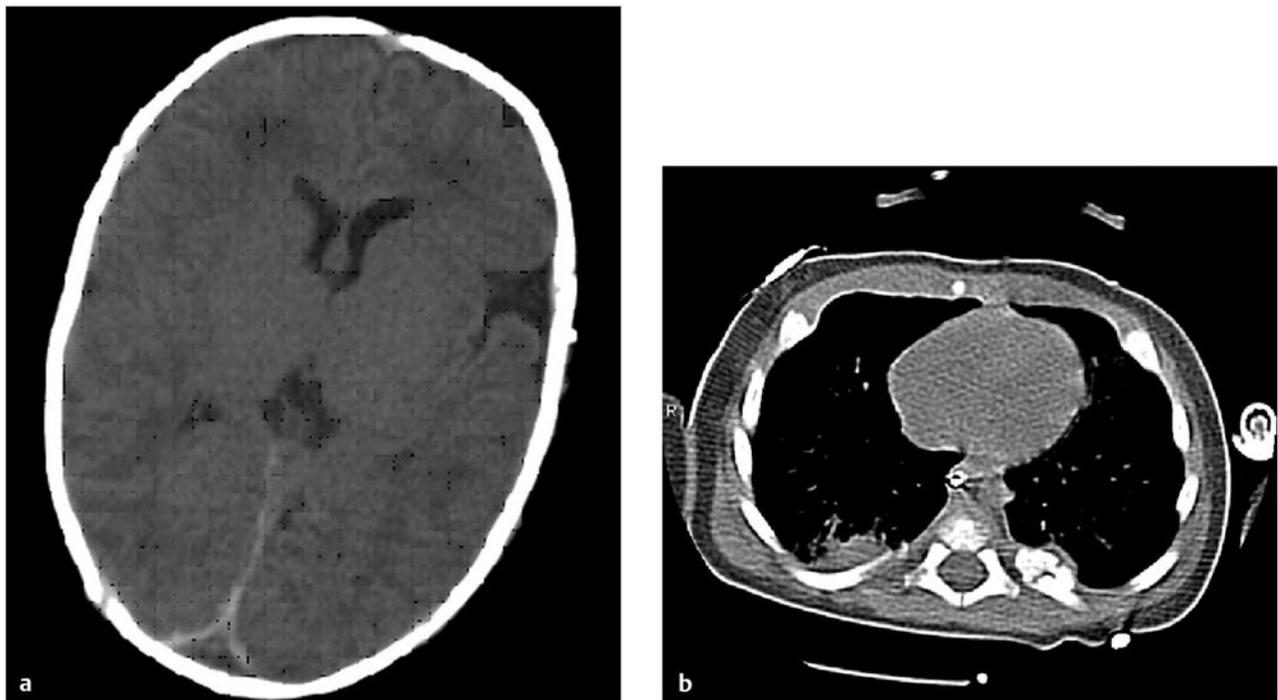


Fig. 52.1 Unenhanced computed tomographic (CT) scan of a 6-week-old baby who was found at home unresponsive with irregular breathing. There was no history of trauma. (a) Axial view through the brain showing interhemispheric blood. (b) CT scan of the chest showing a healing left posterior rib fracture.

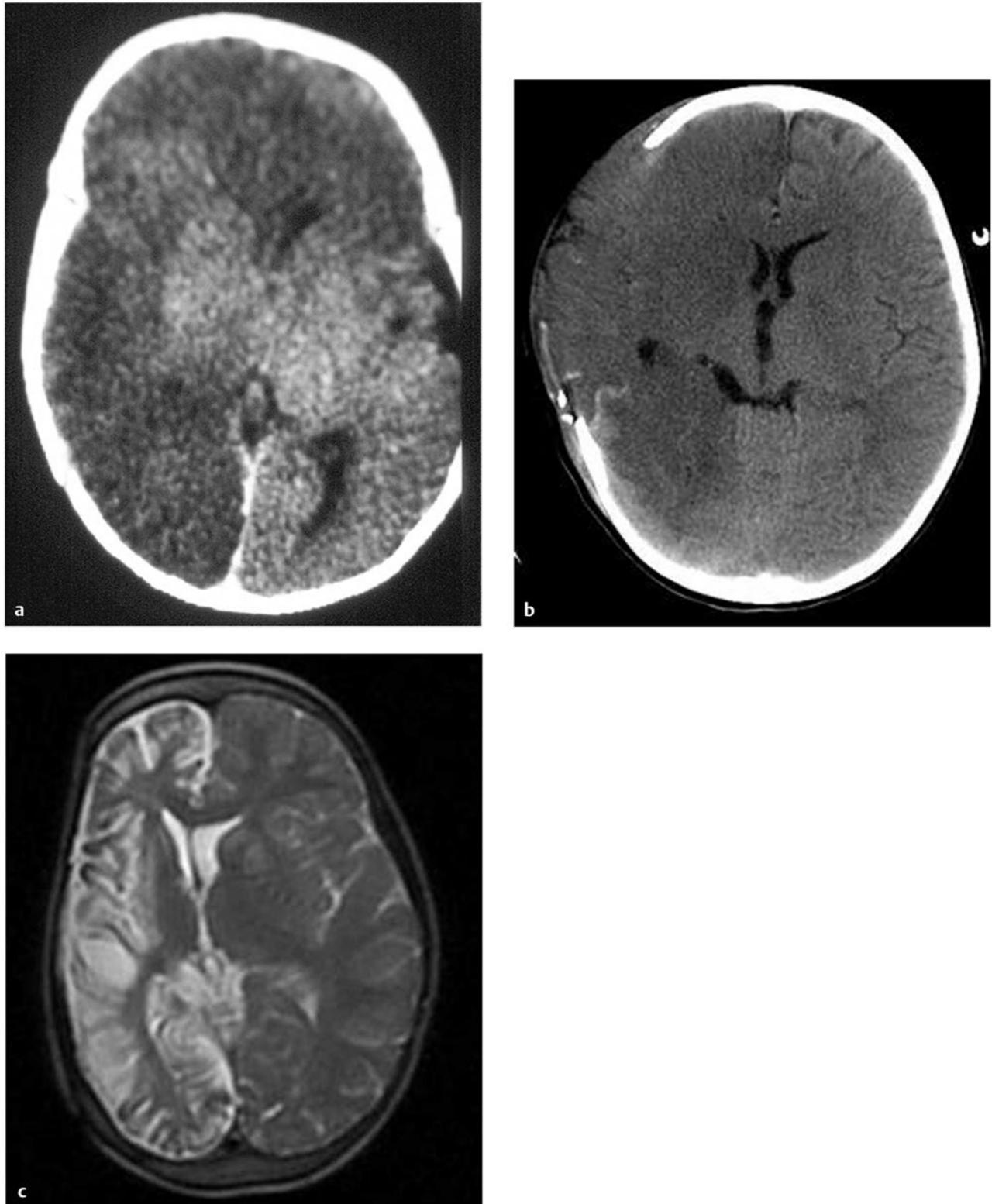


Fig. 52.2 (a) Unenhanced axial computed tomographic (CT) scan showing unilateral hypodensity of the entire hemisphere (“big black brain”) with involvement of the contralateral medial frontal lobe in a child with inflicted injury, likely reflecting subfalcine herniation. (b) CT scan in a child with inflicted injury treated acutely with cranial decompression. (c) Rapid T2 magnetic resonance image 2 years later. Note preservation of the contralateral frontal lobe.

subdural collections, which when identified point the clinician toward a consideration of a traumatic etiology for an enlarging head (► Fig. 52.3). In some children with macrocephaly as the presenting complaint, rapid MR imaging techniques, which do not require sedation (typically, fast-acquisition T2-weighted images in multiple planes), serve as an increasingly utilized means to differentiate chronic subdural collections from the much more common enlargement of the subarachnoid space⁶⁸ (► Fig. 52.4). Skull fractures are noted in approximately 25 to 75% of children, depending on the techniques used to assess them; historically, plain skull films are more likely to diagnose skull fractures than are CT scans, but in the digital era, the resolution of plain films may be decreased, and three-dimensional CT reconstructions with reduced radiation dosage may be the most reliable at present^{56,69–72} (► Fig. 52.5 and ► Fig. 52.6). Some fractures and scalp injuries are visible only at autopsy.^{12,24} Skeletal injuries to the ribs, long bones, or spine occur in 30 to 70% of children with inflicted head injuries.^{69,73} Fractures of the metaphyses of the long bones and to the posterior ribs are highly associated with inflicted mechanisms, and other injuries, such as spiral fractures of the femur, also occur with increased frequency in this setting. Because the identification of unexplained injuries is one of the most reliable adjuncts to a diagnosis of inflicted injury, a full skeletal survey should be performed, rather than a “babygram” (i.e., a single anteroposterior image of the entire infant) or other less thorough survey. Radioisotope bone scan also may be helpful in equivocal cases to identify subtle acute injury, and follow-up plain films can confirm the presence of healing bone injury.⁷⁴ Radioisotope bone scan may identify some skeletal injuries not seen on plain films and may be complementary.⁷⁵

Copy editor, note to Thieme: Caption for ► Fig. 52.7 has been moved to where the figure is first called out. Although evidence of injury to the cervical spine has been described with more consistency in several autopsy series, these injuries (which include extradural and intradural hemorrhages, nerve root injuries, and small parenchymal abnormalities) are rarely visualized on MR imaging.^{12,76–78}

Soft tissue injuries including frenulum tears and patterned bruising (e.g., loop marks, bite marks, or bruises in the pattern of a striking object) or burns may be seen.⁷⁹ Care should be taken to avoid misinterpreting the patterned bruises seen in some folk remedies practiced in various cultures, such as coin rubbing, as inflicted injury.

52.5 Mechanisms and Types of Injury in Infants and Young Children

Part of the confusion in the literature on injury in infants and children arises from semantics—that is, from terminology that is defined differently in different contexts or by different authors. Head injuries can be classified in a number of ways, including by injury type, by mechanism, and by severity. It is worth reviewing the terminology briefly because in the medicolegal context, these semantic differences can be problematic, and the unsuspecting physician acting as a fact or expert witness may find that these terms become a point of controversy during testimony.

First, head injuries may be classified by *pathoanatomical injury type*. This is the “where and what” of a specific injury. Thus, as is obvious to neurosurgeons, an epidural hematoma is located in the epidural space and is a clot, and scalp contusion, skull fracture, subdural hematoma, intracerebral hemorrhage, diffuse axonal injury, and other injury types also follow this “where and what” terminology. It is useful to keep in mind that many if not most clinical traumatic events produce more than one injury type.

Head injuries also may be classified by *mechanism*. These include impact and inertial events, the former requiring contact with the head and the latter reflecting movements of the head and/or brain. Inertial forces may be translational, in which the head moves in a straight line, or rotational (also described as angular), in which the head and/or brain moves around a center of rotation. The specific injuries incurred from a traumatic mechanism depend both on the *type* and the *magnitude* of the specific forces applied to the head and brain. In most clinical injuries, the head and brain are subjected to multiple types of forces at different magnitudes, even during a single event.^{80,81} For example, in a motor vehicle crash, the contact of the head with the dashboard results in focal contact forces at the site of impact, while the movement of the brain during deceleration results in the application of diffuse inertial forces throughout the brain parenchyma. A patient subjected to this mechanism may have both frontal brain contusions resulting from impact forces and diffuse axonal injury from inertial forces related to rapid angular deceleration.

Finally, head injuries may be classified by *severity*. The Glasgow Coma Scale (GCS) and its derivatives for the pediatric population have all been used to categorize acute injuries as mild, moderate, or severe. The original GCS was designed to be used at 6 hours after injury and after resuscitation to compare patients among different centers, and it was validated to be predictive of outcome after head injury in adults when used for that purpose.⁸² However, it has major drawbacks as a predictive tool in infants and preverbal children and is sensitive to influence by sedative and paralytic agents and intubation.⁸³ In addition, in common parlance, laypersons may think of a skull fracture as a “serious” injury, but from the neurologic point of view, a skull fracture may occur with essentially no injury to the brain and so is not “serious” in the sense of expected long-term consequences. Confusion over this sort of terminology can be vexing when neurosurgeons interact with legal or child protection professionals.

In the context of inflicted injury, these terms and classifications may arise with erroneous assumptions that are worth noting. For instance, with respect to pathoanatomical injury types, subdural hematomas are the most common intracranial hemorrhage in inflicted injuries in infancy, but there are different mechanisms that may be associated with subdural hemorrhages and different lesions that may be misinterpreted on CT scans as subdural hematomas.^{64,84} Thus, the presence of something that is or looks like a subdural hemorrhage does not in and of itself confirm a diagnosis of inflicted injury. Likewise, some nonaccidental injuries are “life-threatening,” but so are arterial epidural hematomas, which may arise from low-height falls in infants. Thus, the presence of a “serious” or “life-threatening” head injury does not by itself imply an inflicted mechanism, or even a mechanism that is necessarily inconsistent with

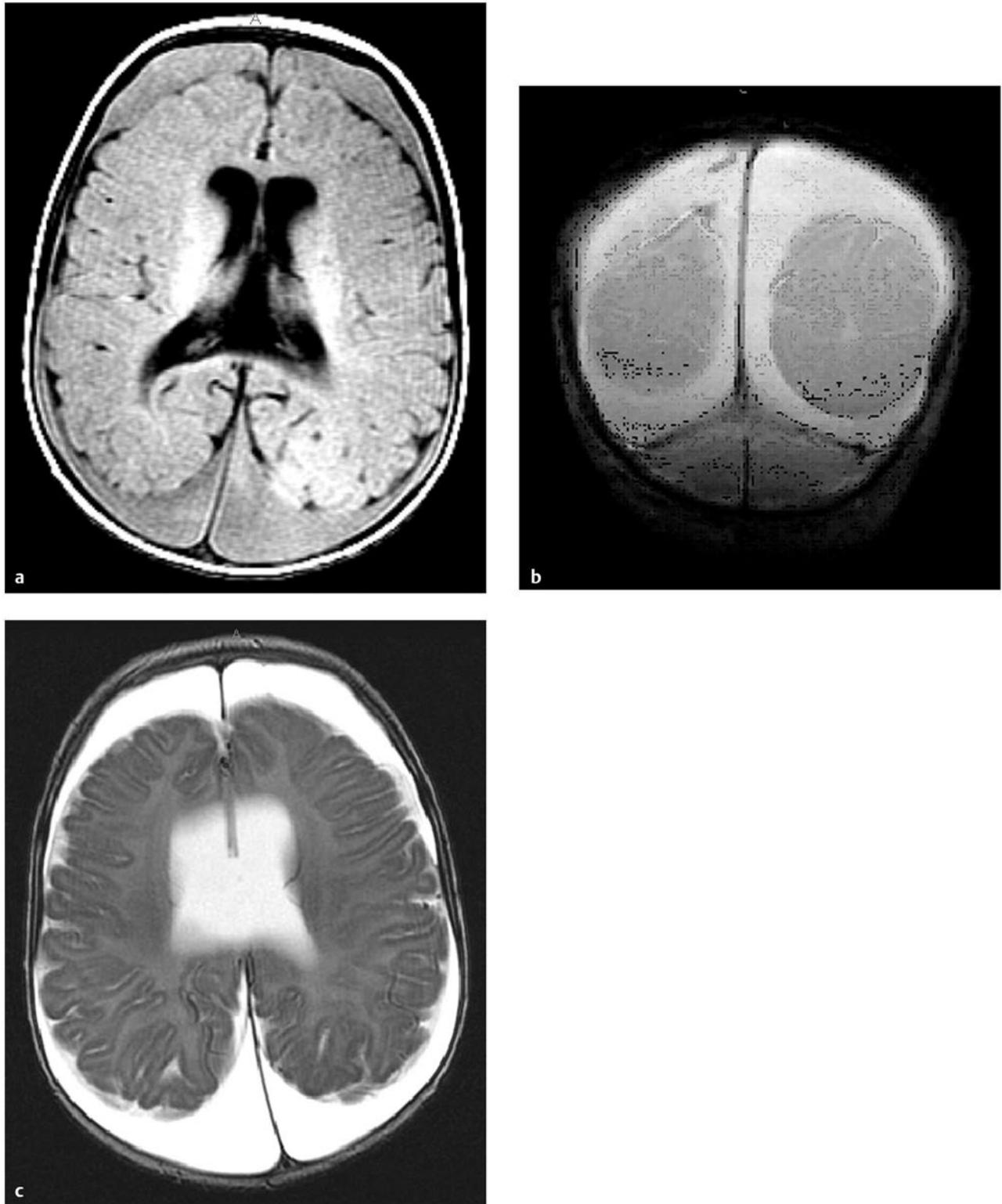


Fig. 52.3 Axial T1-weighted (a), coronal gradient-echo (b), and T2-weighted (c) magnetic resonance images of the brain of a 3-month-old infant with an enlarging head circumference. Note the ruptured parasagittal bridging vein in (b) and the tear in the septum pellucidum, best seen in (c). The infant was also found to have multiple healing fractures. The father, who had been abused as a child, admitted to throwing the infant on the floor and across the room when she cried.

the history given. Our colleagues in the legal profession who do not have a broad experience with the range of head injuries common in accidental and inflicted injuries may not have as complete an understanding of the crossover between these types of terms, which may lead to frustration when the neurosurgeon is called as a witness. Several articles have been written that detail series of injury types resulting from various accidental mechanisms of injury in infants and young children, including falls from beds at home, falls from beds while in the hospital, and falls in stairways and from heights.⁸⁵⁻⁹⁰ Other authors have approached the question of what mechanisms cause what injury at what age by retrospective or prospective studies of

consecutively assessed children admitted or evaluated through emergency departments.^{15,31,91-93} These studies are remarkably consistent in that they show that, with the exception of epidural hematomas, low-height falls in children (generally from household surfaces with a head-to-impact distance of less than about 3 feet) do not result in life-threatening brain injuries. When small focal collections are interpreted on CT scans as subdural hemorrhages, they usually are found in infants who appear clinically well.^{84,91-93} This is why the history of a low-height fall in a child with an acute subdural hematoma and neurologic compromise is generally considered grounds to consider inflicted injury as a possible mechanism of injury.^{16,35,81,94}

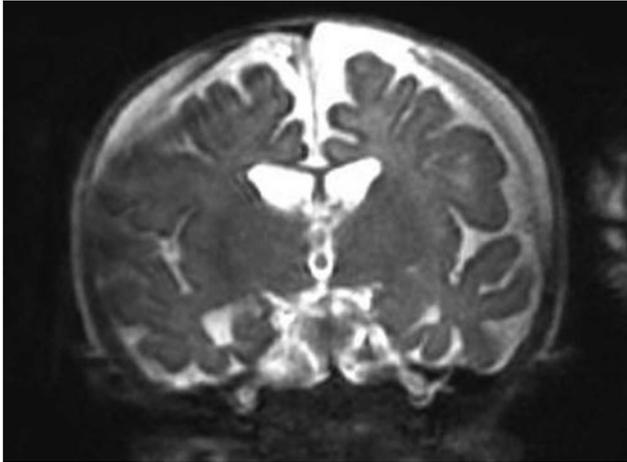


Fig. 52.4 Rapid T2-weighted magnetic resonance (MR) image, coronal view, showing bilateral subdural collections in an infant with an enlarging head. Rapid MR imaging techniques appear to be sensitive in visualizing subdural collections, can be performed without sedation or radiation exposure, and have gained increasing utilization for macrocephaly screening.

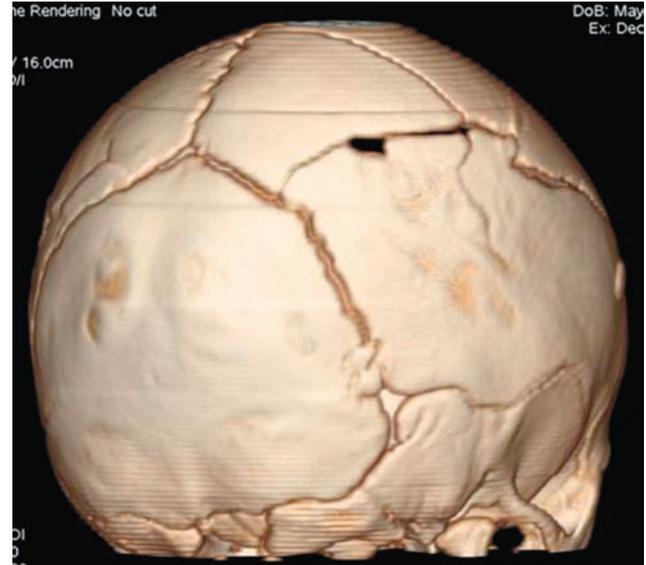


Fig. 52.6 Three-dimensional computed tomographic scan of a child with skull fractures after a reported fall in a bathtub. Note multiple complex fractures. The father later confessed to abuse.

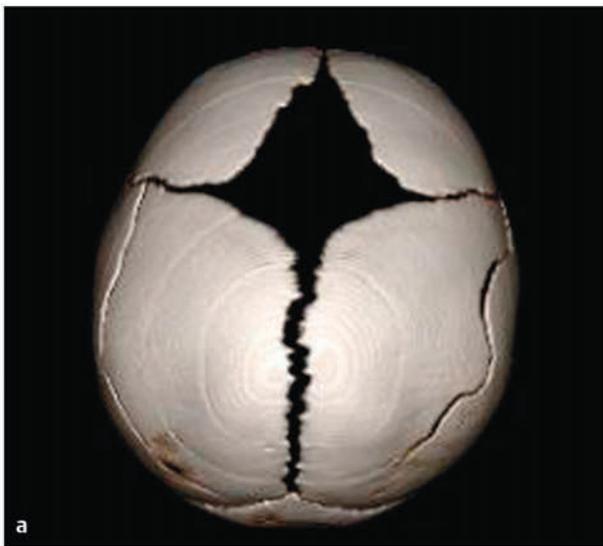


Fig. 52.5 (a,b) Three-dimensional computed tomographic scans of the head of a child dropped while being carried by its mother, who tripped over the family dog. The impact to the child's forehead caused bilateral parietal fractures. Images were acquired with a reduced radiation dose technique.



Fig. 52.7 “Contact” subdural injury. This 16-month-old toddler fell from the side of a basement stairway onto cement. She sustained a skull fracture and an underlying torn cortical vessel, resulting in an acute subdural hematoma, and was minimally responsive on presentation. After evacuation of the hematoma, she made a good neurologic recovery.

An exception to the wide body of literature cited above documenting the relative safety of low-height falls is a paper written by Plunkett that is often quoted by defense experts in inflicted injury cases.⁹⁵ This paper was a retrospective review of data on playground equipment collected by the U.S. Consumer Product Safety Commission (CPSC) National Injury Information Clearinghouse. Data were collected from selected U.S. hospital emergency departments to create a probability sample that could be used to assess consumer product-related injuries. A subset of these injuries underwent more in-depth investigations by CPSC staff. The author of the paper reviewed files in the database for head and neck injuries involving playground equipment that occurred from 1988 to 1999. He found 18 deaths due to falls in children ranging in age from 12 months to 13 years. The article profiles these cases, most of which involve falls from swings, ladders, and platforms. Distances, measured from the body part closest to the ground (not from the head to the ground), ranged from 2 to 10 feet. Most children had skull and/or scalp injuries, and the most common intracranial pathology was subdural hematoma with brain swelling; some children had contusions and/or epidural hemorrhages. In some children, the clinical symptoms were minor initially and then progressed over hours to days. Some children had retinal hemorrhages. About two-thirds of the patients had autopsies. The author concluded that “short-height” falls can cause fatal injuries in children, that

retinal hemorrhages can occur, and that a “lucid interval” may be present.

For neurosurgeons who deal with many traumatic injuries, none of these conclusions is surprising. However, there is a difference between these mechanisms and the histories given in many inflicted injury scenarios, which most often describe low-velocity falls from low heights, usually from a stationary reclining position, so that the distance the head falls is less than 2 feet (the average couch is about 18 inches in height). Playground falls typically happen in older children, there is often an initial velocity in addition to free fall acceleration (such as occurs on swings and seesaws or when children are jumping or swinging on bars), and the fall height of the head itself may be several feet greater than the distances cited for the body part closest to the ground. Contact and other types of subdural injuries (discussed further below), contusions, and intracranial lesions can indeed progress over time as brain swelling occurs, particularly if the seriousness of the injury is not initially recognized. Contusional swelling, hyponatremia, hypoventilation, and seizures can all contribute to a worsening clinical status. Retinal hemorrhages, seen in some of the children reported in Plunkett’s paper, have been previously documented in a number of accidental scenarios, particularly those associated with acute subdural hematoma.^{15,40,42,47}

Because subdural hematomas are so common in cases considered as possibly inflicted injuries, it is worth discussing briefly the different types of subdural hematomas with respect to what structures constitute the sources of hemorrhage and the different mechanisms involved. Although at least one neuropathologist has suggested that the subdural hemorrhages seen in inflicted injury might be due to hypoxia alone,⁹⁶ most researchers continue to assume that the hemorrhages are traumatic in origin. This assumption is based on the frequent finding of additional signs of mechanical injury, as well as the lack of subdural hemorrhage in most cases of hypoxia/ischemia in infancy with other causes. As described below, it may be that more than one mechanism is at work to explain the varied findings encountered.

Classically, convexity subdural hemorrhages in adults are thought to occur from rapid angular deceleration, in which the head stops moving but the brain continues to rotate within the skull. This causes stretching and ultimately rupture of the parasagittal bridging veins, which are avulsed from the cortical surface and bleed into both the subarachnoid and subdural space.^{97,98} In primate experiments, an anterior-posterior (sagittal) plane of rotation is the one most likely to result in bridging vein rupture, and a large magnitude of angular deceleration is required.⁹⁹ Despite the fact that case reports, mostly of older adults in motor vehicle collisions, have documented the occurrence of subdural hemorrhages without contact, in most cases of acute subdural hemorrhage in adults (especially in younger patients), contact is required to create the large angular deceleration forces necessary to rupture cortical bridging veins.^{3,80,99} Under conditions of lower magnitudes of angular deceleration (i.e., those that involve lower velocities and more gradual deceleration), the parasagittal veins may stretch but do not fail. Contrary to Caffey’s original descriptions, it has been reported that in the majority of cases of inflicted injury in infants and young children, signs of cranial impact are evident with careful radiologic and forensic techniques, including skull fractures and

scalp hematomas.^{24,100–102} When impact forces are dissipated over a wide area against a deformable skull, surface contact injuries may not be evident clinically or radiologically, or contact injury may not occur at all.

A great deal of effort has been expended by persons in the field of child maltreatment to address the question of whether shaking alone can or cannot cause serious injury in infants and young children. This question revolves around the specific mechanism of injury as well as the types and magnitude of forces and the injury threshold necessary for the particular types of injuries seen in cases suspicious for inflicted trauma to occur. There are arguments on both sides of this debate arising from clinical, medicolegal, and biomechanical sources.^{10,101–109} One factor that clouds the debate arises from the fact that many clinical and autopsy series concluding that shaking has occurred rest on the assumption that the absence of findings of impact necessarily implies that shaking took place. In fact, impact and rapid deceleration both may occur without visible sequelae of direct impact. This fact has been documented in series of children with clear accidental trauma.¹¹⁰

With respect to the *magnitude* of deceleration, biomechanical studies using anthropomorphic surrogates have shown that shaking alone appears to correlate with relatively small angular deceleration forces in comparison with inflicted impact to the head, with impact causing deceleration 30 to 50 times greater than that caused by vigorous shaking alone.^{24,103} The forces generated by shaking, when scaled for injury thresholds in young adult nonhuman primates, do not reach the concussion threshold. In contrast, impact events span the range of concussion, subdural hemorrhage, and even diffuse axonal injury.²⁴ Inflicted impact in a recently reported model of a 6-week-old infant was associated with significantly greater angular deceleration than that caused by a fall from 5 feet in which the head struck cement.¹⁰³

Finally, the question of whether infants and young children have a lower *threshold for injury* in the context of shaking compared with older children, adults, primates, and other sources of comparison is still under study. Some data from immature large animal models suggest that the threshold for axonal injury resulting from angular forces may be lower during immaturity, whereas younger subjects may be more resistant to damage from focal injury and subdural hematoma.^{111–113}

At present, although different opinions exist, it is probably accurate to say that the exact mechanism and threshold necessary to cause *any* injury to the intracranial contents, as well as the amount and type necessary to cause *severe or fatal* brain injury, remain incompletely understood. This is particularly true when the contributions of repetitive injury, hypoxic/ischemic insult, and/or cervical spine injury are also taken into account.^{60,67,78,107,111,114–116} This is not to say, however, that nothing has been learned about mechanisms of injury and the typical sequelae of injury, as will be further discussed below.

Finally, challenges have been raised about whether the presence of subdural hemorrhage necessarily implies a traumatic mechanism or whether subdural bleeding can occur from hypoxic/ischemic stress, coughing, or vomiting.^{96,117} Although such explanations have been proposed, and some autopsy cases used to explore these possibilities, to date such occurrences do not fully match the types of clinical injuries typically seen in suspected cases of inflicted injury, and these mechanisms have not been found to be associated with subdural hemorrhage in

series of children with medical conditions causing repeated coughing or vomiting.¹¹⁸

In acute inflicted injuries, although the questions of which vessels rupture and what mechanisms are required to cause acute subdural hemorrhage are still debated, it seems likely that different mechanisms may be at play in different cases.^{11,96} Chronic subdural collections are even more problematic with respect to mechanism; the likelihood of a nonaccidental etiology for chronic collections remains a matter of debate, with estimates ranging from 46 to 68%.^{94,119} In elderly patients with cortical atrophy or children with shunted hydrocephalus, it has been observed that relatively mild blows to the head may result in subdural hemorrhage; it is generally hypothesized that enlargement of the subarachnoid space results in greater stretch of the bridging vessels. However, in children with so-called “benign external hydrocephalus,” in which the subarachnoid spaces are enlarged, subdural hemorrhage appears to occur rarely.^{64,120} Whether small collections that are minimally symptomatic may predispose to recurrent bleeding, with symptom onset after relatively mild trauma, remains a point of debate in the defense world. However, the frequency with which young children fall repeatedly without catastrophic hemorrhage seems to argue against this “two in a row” explanation for serious brain injuries potentially resulting from low-height falls. The term *second impact syndrome* is used to describe the rare occurrence of highly morbid or fatal consequences after repeated sports-related contact injuries in adolescents and young adults.^{121–123} These athletes are found to have subdural hemorrhages and/or severe acute brain swelling accompanied by acute unconsciousness immediately or within minutes of second contact. To date, there is no convincing evidence of a similar phenomenon resulting from low-height falls (less than 3 to 4 feet) in infants and young children.⁶⁴

One difference between infants and older children and adults is the relative deformability of the infant skull. Thus, other surface vessels besides the parasagittal bridging veins may be stretched or torn during certain kinds of events. Small convexity, posterior fossa, and tentorial subdural hemorrhages may occur during birth, and skull deformation from static loading during crush injuries may lead to collections at these sites.^{124,125} It has been hypothesized that deformation of the back of the head due to inflicted impact might rupture posterior draining veins, thus accounting for the high frequency of posterior interhemispheric fissure hemorrhages.¹¹ In a series of infants younger than 2 years of age with subdural hemorrhages due to motor vehicle collisions, skull fractures were seen in the majority, and half had other types of parenchymal brain injury and varying levels of depressed consciousness. The subdural collections were seen most commonly along the falx and frontoparietal convexities, and retinal hemorrhages were sometimes seen.¹²⁶

Other mechanisms that can cause subdural bleeding include contact subdural injuries, which can occur in adults and children from a focal blow over a cortical vessel (► Fig. 52.4). Venous epidural hemorrhages, usually associated with fractures, may be indistinguishable from subdural hemorrhages on CT scan. So-called “disappearing subdurals” may occur in children after falls and likely represent focal subarachnoid hemorrhages that are diluted rapidly and resolve over a day or two after injury.⁸⁴

In summary, acute subdural hemorrhages in infants and young children that are accompanied by significant acute neurologic deficits (such as coma) appear to result from accidental

mechanisms that require more force than those associated with low-height free falls. Although exact thresholds are still not available, there are clinical and experimental data to indicate that free falls from heights such as those of furniture (head-to-floor distance not more than about 3 feet) can cause skull fractures, epidural hematomas, and perhaps other focal extra-axial collections, but they do not appear to be sufficient explanation for the phenomenon of acute subdural hematoma, brain swelling, and death.^{15,32,81,91,92,103}

52.6 Treatment

The medical and surgical management of acute inflicted brain injury is no different from that for injury associated with other mechanisms. It may be helpful to note that an infant who does not cry or show a vigorous facial expression to a trapezius pinch or other painful stimulation is likely to have a significant depression of cortical activity, which may be reflective of severe injury.⁸³ The general principles of airway, breathing, and circulatory support apply to these patients. Collaboration with colleagues in general surgery can minimize the chance of missing additional injuries, such as abdominal trauma. Serial routine laboratory tests, including hemoglobin, electrolytes, and coagulation studies, will help identify evolving complications.¹²⁷

Because seizures are common and may have subtle clinical manifestations, anticonvulsants should be considered even if seizures are not clinically apparent.^{9,26,59} Hemorrhages with significant mass effect are uncommon, but in this instance, evacuation may be considered. Some authors advocate creating “dural slits” to allow blood to extrude without creating difficulty in closure because of excessive brain swelling. Others have used decompressive craniectomy as a way of managing brain swelling, which may be considerable in these cases.^{128–130} Although prospective trials are lacking, early hemicraniectomy may help limit damage to the contralateral hemisphere in cases of unilateral severe damage with brain swelling (unilateral “big black brain”)^{60,130} (► Fig. 52.2).

As previously mentioned, the poor outcome seen in many patients with inflicted head injuries, particularly those with bilateral diffuse hypodensity, may influence the degree to which extraordinary interventions are applied.^{63,131} Elevations in cerebrospinal fluid markers of brain injury are particularly pronounced in infants with inflicted injury if they have previously been treated with ventriculostomy; whether this reflects a specific vulnerability related to patient age or the significant parenchymal damage from trauma and/or hypoxia/ischemia remains uncertain.^{132,133}

52.7 The Role of the Neurosurgeon in the Medicolegal Investigation of Inflicted Injury

Most children's hospitals and academic medical centers have a child protection team that takes on the responsibility of investigating and reporting suspected abuse. The neurosurgeon may be asked to consult as to whether a given patient's injuries appear consistent with the mechanism reported. Several workers in the field have attempted to address this problem with sys-

tematic approaches or algorithms to assist in this determination, based on the body of clinical and experimental evidence surveyed in previous sections.^{15,81,134,135}

Clinicians may be requested or required to participate in civil or criminal proceedings. Civil proceedings generally deal with the disposition of the child, whereas criminal cases determine if a crime has been committed and by whom. It should be kept in mind that the level of suspicion for inflicted injury determined by the medical team typically falls into one of three main categories: consistent with accidental trauma, presumptive for inflicted injury, or “suspicious but not presumptive (indeterminate).” Part of the conflict that often occurs between the medical and legal professions in this arena arises from the general principle that the medical team tends to use three categories of level of suspicion, whereas the legal system tends to prefer a more dichotomous determination, particularly in criminal matters. Thus, the neurosurgeon may feel pressured into saying “it was” or “it wasn't” abuse, when the most honest and complete answer in a particular case is “it may have been, but we can't tell for sure.” Although the intermediate category may not be sufficient for criminal prosecution, it by no means precludes child protective service involvement, with the goal of keeping the patient and/or other children safe from harm. In criminal proceedings, questions about the degree of certainty regarding the etiology of the findings are common. In addition, in order to prosecute or defend specific individuals, questions about forces required, intent, alternate explanations, timing, and the possibility of a “lucid interval” during which the accused may have simply unwittingly taken over care are frequently raised.^{11,64,136}

With respect to court appearances, neurosurgeons may be called as fact witnesses or as expert witnesses. In some states this distinction is clear, and the treating physician can decline to comment on any but the basic facts of the case relevant to his or her care of the child. In other states, the treating physician can be admitted as an expert by the judge even if he or she has requested to provide fact witness testimony only, and can be compelled to provide opinions on the mechanisms responsible for the injuries to the child.¹³⁷ It may be helpful under these circumstances to keep in mind that the field of inflicted head injury is a specialized and controversy-ridden one, and that to expect all neurosurgeons to be fully familiar with all the relevant clinical and basic research is unreasonable. The physician and patient are best served when the witness provides a full and accurate testimony without speculation and resists being pressured into conjecture or “best guess” answers, especially if the experience of the witness in this aspect of the field is limited. Conversely, when the injury syndrome is clearly consistent with inflicted injury (e.g., healing skeletal fractures, acute life-threatening subdural hemorrhage with evidence of contact injury, severe bilateral retinal hemorrhages, and no history of trauma), the neurosurgeon can express these views with confidence.

52.8 Prevention

As understanding of inflicted injuries in infants and young children has evolved, prevention efforts have changed, as well. Early campaigns were directed at parents, particularly mothers, to educate them to “never ever shake a baby,” usually via pamphlets and other educational materials provided at well-child checkups.^{138,139} Home visits to at-risk families of newborns

have received increasing attention as a preventative strategy.¹⁴⁰ More recent efforts have focused on the neonatal period; mandatory education is provided while infants are still in the newborn nursery, and both parents are encouraged to sign a contract promising that they will not use physical force when frustrated by crying or other infant behavior.¹⁴¹ Because many perpetrators are male friends of the mothers of infants, other potential targets for prevention efforts would seem to be young men, perhaps through a school setting, and mothers, who need to be educated to be cautious when deciding to leave their infants in the care of a boyfriend.

52.9 Conclusion

Although it is tempting to be nihilistic about inflicted head injuries, it is probably fair to say that aggressive management in infants who do not present with bilateral diffuse hypodensity likely improves outcome, as it does in accidental head injuries.^{60,142} Over time, more research and open-minded data gathering and analysis will help shed light on the necessary forces and circumstances required to cause different types of injuries in children of different ages. However, at present, the diagnosis of inflicted injury rests on a constellation of specific findings in association with a specific history or lack thereof. As in accidental trauma, prevention is key. The neurosurgeon plays a significant role here both in prevention efforts in general and in preventing injuries to other children who might be the next victim of an unrecognized perpetrator. Objectivity and compassion for the patient, family, and potential future victims must all be brought to bear in these difficult cases.

Pearls

- Inflicted injury is the most common cause of traumatic mortality in infants.
- The most common constellation of findings in children with inflicted head injury includes subdural hemorrhages with or without scalp contusion, skull fracture, retinal hemorrhage, and skeletal injury.
- Because children may present with a variety of injury types resulting from a variety of mechanistic causes, the terms *inflicted injury* and *nonaccidental injury* are preferable to those implying a specific single mechanism (such as *shaken baby syndrome*).
- The most common history is no history of trauma (infant presenting because of symptoms such as lethargy or seizures) or a history of a short-height free fall.
- Infants may present with varying levels of consciousness, ranging from normal to comatose. An infant who does not cry or grimace in response to painful stimulation can be considered to have cortical impairment.
- Apnea and seizures are common, and seizures may be subclinical.
- Infants who present with unresponsiveness and whose imaging shows bilateral hemispheric hypodensity have high morbidity rates and uniformly poor outcomes. Infants with lesser degrees of injury have variable outcomes. Early hemicraniectomy has gained increasing use in children with the unilateral form of severe brain swelling associated with subdural hematoma.

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53 Accidental Head Injuries in Children

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The management of traumatic injuries has been the focus of medical writings since the earliest known medical document—the Edwin Smith Surgical Papyrus.¹ This 3,000-year-old papyrus contains the writings of the ancient Egyptian physician Imhotep, in which he details the rational management of 48 medical cases, 27 of which are cases of traumatic injury. Our current medical practice can be traced back to Imhotep's rational, experienced (“evidence-based”) approach to medicine.

This chapter focuses on accidental head injuries in children, drawing from the literature and the recently updated “Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents—Second Edition.”² The incidence, mechanisms, and outcomes of accidental traumatic brain injury (TBI) in children are distinct from those in adults and vary with the age of the child. They also vary from those of nonaccidental TBI in children, who likely represent a unique and distinct group and are reviewed in Chapter 52. In addition, the physiologic and pathophysiologic responses of children to trauma vary with age, and therefore management must be age-specific. A practical approach to the diagnosis and management of accidental traumatic injuries to the developing nervous system is presented in this chapter. Other chapters in the section on trauma deal specifically with such topics as penetrating head injuries, hematomas, critical care management, rehabilitation, and outcomes.

53.1 Epidemiology

Unintentional injuries are the leading cause of death in children. They account for at least a third of deaths in children aged 1 to 14 years and half of those in older adolescents.³ Of all types of traumatic injuries, those to the brain are the most likely to result in death or permanent disability. Among children aged 0 to 14 years, TBI results in an estimated 2,174 deaths annually, 35,135 hospitalizations, and 473,947 emergency department (ED) visits. The annual death rate from traumatic injury in children younger than 4 years is 5 per 100,000. The death rate is higher for children younger than 4 years than for those 5 to 14 years of age. The higher traumatic injury death rate in younger children may sadly reflect the number of inflicted injuries in infants and young children because these figures do not distinguish accidental injury from abusive injury. In adolescents and young adults 15 to 19 years of age, the death rate rises to 19 per 100,000, approaching the rate of death by TBI for young adults.⁴

The most common mechanisms of pediatric TBI vary by age group. Developmental milestones for movement and ambulation are reflected in the way children are injured. Falls are the leading cause of TBI in children younger than 14 years.⁵ Children younger than 4 years of age are injured primarily by falls but are also vulnerable to inflicted injuries and motor vehicle crashes. Children 4 to 8 years of age are injured in falls and motor vehicle crashes but also become more at risk for other transportation-related injuries (e.g., bicycles, as pedestrians struck

by cars, etc.). The leading cause of death past the age of 14 is motor vehicle crashes, which kill more teenagers than all other causes combined.^{6,7}

53.2 Types of Accidental Head Injuries

Accidental head injuries in children result in a spectrum of traumatic injuries to the scalp, skull, meninges, and brain that are comparable to those in adults but differ in both pathophysiology and management. The highly vascular scalp is a potential source of major blood loss. Whereas a small loss of blood volume in an adult trauma victim can be trivial, the same blood loss can readily lead to hemorrhagic shock in a newborn, infant, or toddler. This may occur without overt external bleeding in infants and young children. By that token, the presumed plasticity of the brain that is lost with development may provide an outcome advantage for the developing brain compared with its adult counterpart.

Advances in technology impact the delivery of medicine by helping physicians to efficiently evaluate, diagnose, and transfer severely injured patients. Computed tomography (CT) has become widely available and affordable. The luxury of such technology should augment, not substitute for, clinical skills and judgment. It is estimated that for every 700 head CTs ordered, one additional fatal cancer occurs that can be attributed to radiation exposure.⁸ The judicious use of CT screening and follow-up examinations is important for cost control and patient safety. A recent prospective study of 42,412 children with minor blunt head trauma conducted by the Pediatric Emergency Care Applied Research Network (PECARN) validated a set of predictive rules to identify children who can be observed without CT. Among patients without altered mental status, scalp hematoma, loss of consciousness, severe mechanism of injury, signs of skull fracture, severe headache, or abnormal behavior, fewer than 0.05% had a clinically significant TBI.⁹ It is likely that a significant portion of CT examinations ordered for children by EDs may not be medically necessary.

The incidence of cervical spine injury in the pediatric population with blunt trauma in the National Emergency X-radiography Utilization Study in Blunt Cervical Trauma (NEXUS) was 1%.¹⁰ Although rare, the morbidity and mortality associated with spinal cord injury require accurate and rapid identification of affected patients. The biomechanics of the developing spine also predispose young children to spinal cord injury without radiographic abnormality (SCIWORA).¹¹ The Trauma Association of Canada (TAC) has recently published the first evidenced-based consensus guidelines for clearance of the cervical spine in pediatric trauma patients. These guidelines recommend applying NEXUS criteria with the addition of 45-degree neck rotation in order to clear the cervical spine, reserving CT or magnetic resonance (MR) imaging for those with abnormalities on X-ray and neurologic examination or with neck pain. Validation of these guidelines with prospective data is expected to take several years.¹²

53.2.1 Injuries to the Developing Skull

The developing skull is thinner, more pliable, and more easily deformed than its mature counterpart. Open sutures provide the skull with some movement and can offset some rise in intracranial pressure (ICP) by expanding the intracranial volume.¹³ Skull injuries can be classified as nondepressed (linear), depressed, elevated, basilar, or growing.

Linear Skull Fractures

Skull fractures are common injuries in young children. Linear skull fractures are the most common abnormal radiographic findings identified in children after head injury.¹⁴ Linear fractures in children may be associated with hemorrhage or significant underlying brain injury, but they usually are not. Complex fractures (i.e., those that are multiple or stellate or that cross a venous sinus) are more likely to be associated with an underlying brain injury or hemorrhage.

Linear fractures represent an injury of sufficient energy that has been dissipated by the skull. The vast majority of linear skull fractures in young children are caused by falls. Anyone who has spent time with toddlers or young children recognizes that falls are extremely common events, even in those younger than 6 months. In a large population-based survey study of 11,466 infants younger than 6 months, there were 3,357 falls in 2,557 children. Despite the large number of falls, of which 53% were from a bed or a piece of furniture, only 21 falls (<1%), resulted in a concussion or a fracture.¹⁵

Linear skull fractures can readily be diagnosed by plain radiography; however, the role of plain radiography in trauma is limited. Clinical criteria should be used to distinguish those patients with risk factors significant enough to warrant computed tomography (CT) from those who can safely be observed without imaging. The importance of a linear fracture is the potential for an associated intracranial pathology.^{16–18} Because of ease of acquisition, availability, relatively low cost, and high sensitivity, CT is the standard test to identify intracranial hemorrhage and fracture in children with significant head injury.^{19,20} Occasionally, CT will miss an axially oriented fracture that falls within the plane of the CT scans. Although uncommon, this problem can be avoided by careful inspection of the CT scan scout image.

The vast majority of linear skull fractures require no treatment and heal without sequelae. Children with an isolated, uncomplicated skull fracture and a normal neurologic examination do not require hospital admission. They can be followed at home after a brief period of observation in the ED, provided that the home situation is reliable and caregivers can return promptly in the unlikely event that deterioration occurs. Admission is prudent for patients with persistent vomiting, significant scalp swelling (which can lead to anemia, especially in infants younger than 6 months of age), neurologic deficits, intracranial injury on CT, or suspicion of child abuse.^{21–23}

Growing Skull Fractures/Leptomeningeal Cysts

Growing skull fractures, or leptomeningeal cysts, are a rare but well-recognized complication, occurring in approximately 1% of children with skull fractures.²⁴ Skull fractures associated

with an underlying dural laceration are the essential substrate of growing skull fractures.²⁵ The growing brain, or perhaps simply the normal pulsations of the brain transmitted through cerebrospinal fluid (CSF), results in herniation of the brain through a dural laceration. Over weeks to months, the edges of the fracture are eroded and/or remodeled, becoming smooth and widening (much as a flowing river erodes its banks). The most common location for growing skull fractures is the parietal region, but they have been described in the orbit and posterior fossa,²⁶ skull base, and anterior fontanel,²⁷ and also as a complication of craniofacial surgery.²⁸ A growing skull fracture presents as a soft, pulsatile mass beneath the scalp, with seizures, or with a progressive neurologic deficit. The diagnosis can be made by skull X-ray in most cases. CT and MR imaging are more sensitive in diagnosing growing skull fractures and can be helpful in identifying the presence of hydrocephalus or an associated porencephalic cyst.²⁹ The treatment of growing skull fractures involves repair of the dura, which invariably requires a dural graft. The dural defect always exceeds the bone defect, which must be taken into consideration when the craniotomy flap is planned. Cranioplasty is also necessary and should be performed with autologous bone whenever possible. A shunt is indicated only when there is associated hydrocephalus, not as a primary treatment for a growing skull fracture. Growing skull fractures should not be allowed to go untreated because the delayed onset of neurologic complications and cranial deformity have been reported.³⁰

Depressed Skull Fractures

Depressed skull fractures are relatively common in children, accounting for approximately 10% of all skull fractures.³¹ Like linear fractures, most depressed fractures, in which the scalp is intact, do not require surgical intervention. This nonsurgical approach does not appear to increase the risk for seizures or neurologic dysfunction, or to result in greater cosmetic deformity.³² Exceptions may be fractures with a suspected dural laceration or significant underlying brain injury, or fractures in locations of cosmetic importance. A unique subset of depressed fractures in infants and neonates are known as ping-pong fractures. Usually, ping-pong fractures are the result of traumatic deliveries, malpositioned forceps deliveries, or short-distance falls. Most ping-pong fractures involve the parietal bone. When small, these fractures will frequently remodel under the influence of the rapidly growing infant brain without intervention. Although the complication rates are similar for simple depressed skull fractures whether they are treated with observation or surgery, the application of a breast pump or vacuum suction has been reported to be a safe and effective alternative for achieving prompt recovery.³³ Larger ping-pong fractures are easily elevated with a small linear incision, a bur hole, and a Penfield elevator, relieving the anxiety many new parents experience while waiting for the deformity to remodel on its own.

Compound or open depressed skull fractures (i.e., those in which the scalp is lacerated) should in most cases be explored, debrided, and repaired. Compound fractures are more often associated with an underlying dural or brain injury and a worse overall prognosis.³⁴ Repair of a compound depressed

skull fracture should include a return of the bone fragments to the defect whenever possible. This approach does not appear to increase the risk for postoperative infection and avoids the need for cranioplasty in the future.³⁵ Prophylactic antibiotics beyond the immediate perioperative period, although used frequently in practice, do not appear to reduce the risk for infection.³⁶

A variation of the depressed skull fracture known as an elevated skull fracture has also been described. Elevated skull fractures result from a high-energy impact with a sharp object that elevates the flap by lateral and tangential force vectors or from direct retrieval of a sharp weapon. Once thought to occur only in adults, elevated skull fractures have been reported in children. These unusual fractures are almost always compound and should be managed as a compound depressed fracture with early debridement, reduction, and repair of the underlying dura. Patients with fractures due to a severe mechanism often present with neurologic complications; however, delayed deterioration is also a risk with simple elevated fractures.^{37,38}

Basilar Skull Fractures

Basilar skull fractures occur in children at approximately the same frequency as in adults, accounting for 15 to 19% of skull fractures.³⁹ CSF leak, via the ear or nose, occurs in about a quarter of the cases and most often stops without intervention. Elevating the head, as well as avoiding straining or any manipulation of the ear or nose, is usually all that is required. In those children (approximately 20%) in whom the leak persists beyond the second or third day after injury, a lumbar drain may be used if not otherwise contraindicated. Prophylactic antibiotics play no role in preventing meningitis in patients with a posttraumatic CSF leak, and their use may actually result in infection by unusual or drug-resistant organisms.⁴⁰⁻⁴²

Persistent CSF leak after a basilar skull fracture that does not respond to a trial of lumbar drainage requires surgical repair. The presurgical assessment should include MR imaging, which is used to exclude posttraumatic hydrocephalus as well as to visualize the site of the leak. Disruption of the skull base or posterior wall of the frontal sinus and leakage of CSF through a dural defect are readily seen on T2-weighted MR imaging. Thin-section CT is also useful to assess fractures of the skull base and for surgical planning, but it is not a reliable method to identify the site of CSF leak. Radioisotope cisternography with nasal pledgets and CT after contrast cisternography can be used to identify the presence and location of a CSF leak, respectively, but are now rarely needed in the era of MR imaging. Operative repair requires adequate exposure of the fracture site, dural repair, and depending on the size of the fracture defect, a bone graft to support the duraplasty and reconstruct the skull base. Lumbar drainage can be helpful to obtain adequate exposure of the fracture site and to decrease the chance of a persistent CSF leak through the dural repair.

All of the structures of the skull base are potentially at risk after a fracture of the skull base. The carotid artery, venous sinus, cranial nerves, and middle ear structures may be injured, and depending on the location of the fracture, attention should be given to the structures at risk based on the course of the fracture.

53.2.2 Injuries to the Developing Brain

TBIs can be divided into primary and secondary injuries, as well as injuries that are focal or diffuse. Primary TBIs are those injuries that are a direct result of the dissipation of the energy of the traumatic force in the brain. Examples of primary brain injuries are contusion, laceration, hemorrhage, and axonal disruption. Secondary brain injuries result from factors that cause further damage to the brain; these occur as a response to, or result of, the primary traumatic injury and the physiologic derangements that follow. Secondary insults or the contributors to secondary injury are hypoxemia, hypotension, cerebral edema, and elevated ICP.

Traumatic Intraparenchymal Hemorrhage

Traumatic intraparenchymal hemorrhages, also known as brain contusions, are primary brain injuries that result from direct trauma to the brain at the point of impact. Focal contusions may also be the result of impact from an overlying fracture or a deceleration injury as the moving brain strikes the inner table of the skull. The injuries may occur at the point of impact (*coup*) or opposite the point of impact (*contrecoup*). Typically, focal contusions occur over the basal frontal or petrous regions and the frontal or temporal poles. The vast majority of focal hemorrhagic contusions do not require surgical intervention unless they are associated with a compound fracture or if they are of sufficient size to require evacuation. Serial CT and close neurologic observation in a monitored setting are required for patients with focal hemorrhagic contusions. A retrospective cohort found that 28.5% of patients with abnormalities on initial CT who underwent repeated examinations within 24 hours had had a radiographic progression. Intraparenchymal, subdural, and epidural hematomas or cerebral edema should be managed as a high risk for deterioration.⁴³

Concussion and Diffuse Axonal Injury

Diffuse injuries to the brain are the result of deceleration or angular acceleration injuries to the head. The spectrum of diffuse brain injury ranges from subclinical concussion to severe diffuse axonal injury. In its mildest form, diffuse brain injury is exemplified by the remarkably common concussion. It has been estimated that 144,000 ED visits for children younger than 19 years have a discharge diagnosis of concussion.⁴⁴

The hallmark of concussion is a brief (seconds to minutes) loss of consciousness. Although a loss of consciousness is sufficient to diagnose concussion, it is not necessary. CT of the brain is usually normal. There can be a period of confusion or amnesia afterward. Concussion is frequently associated with vomiting in children, which may necessitate admission to the hospital. Efforts have been made to grade the severity of concussion based on the length of loss of consciousness, the presence and duration of amnesia, and errors in mentation.⁴⁵⁻⁴⁷ The subtle cognitive, neuropsychological, and physical consequences of concussion are now recognized more often as a result of the development of grading systems, but none of the grading scales has been validated in children. The sequelae are more readily identified after repeated concussions and, not surprisingly, in those who are more thoroughly tested.

Growing public awareness of concussion and perceived “minor” TBIs has been accompanied by a rise in ED visits for sports-related TBIs in the United States. In 2009, there were 248,418 ED visits for sports-related TBIs, an increase of 62% from 2001. Seventy-one percent of patients seen in the ED for recreational or sports-related TBIs are male. Activities associated with the highest incidence of nonfatal TBIs from 2001 to 2009, according to data from the Centers for Disease Control, are bicycling, football, playground activities, basketball, and soccer. However, the number of mild and nonfatal TBIs is likely much higher because these statistics do not account for the many unreported or unrecognized injuries.⁴⁸

Concern exists regarding the cumulative effects of repeated concussion and the risk for catastrophic “second-impact” types of injury. The long-term sequelae of a single concussion on the developing brain are unknown, although most patients are expected to make a full recovery. Evidence-based guidelines for the management of concussion are lacking, but cognitive and physical rest with a gradual return to activity and careful observation of symptoms are advocated. Children should not return to activities that entail a risk for further injury until their memory, behavior, cognition, and neurologic examination have returned to normal.^{49,50} Difficulty arises with young, overachieving athletes and their parents, who insist on putting themselves at risk for further injury by returning to play. There is room for better collaboration among schools, parents, coaches, and physicians to minimize the impact of concussion. Recognition of this fact has resulted in the passage of laws in most states mandating the evaluation of any school-aged athlete suspected of having a concussion and clearance before the athlete may return to play.⁵⁰

On the continuum of diffuse brain injury, at the opposite end of the spectrum from the simple, uncomplicated concussion is diffuse axonal injury. This is thought to be caused by shearing forces between gray and white matter or within subcortical regions as a result of rotational or angular acceleration and deceleration forces. In the early days of CT, patients with diffuse axonal injury presented in a coma with abnormal posturing. Their CT scans were described as normal or as exhibiting small punctate hemorrhages of the gray–white junction, brainstem, or corpus callosum. Today, the diffuse nature of this type of injury is readily evident on MR imaging, which can reveal widespread punctate areas of signal abnormality or subtle hemorrhage felt to reflect axonal injury.⁵¹

Patients with diffuse axonal injury are usually the victims of high-velocity crashes; children with this injury are typically pedestrians or cyclists hit by cars, or passengers in motor vehicles involved in high-speed crashes. In infants and toddlers, these mechanisms may also be associated with craniocervical injuries because of the large size of the head relative to the body, lax spinal ligaments, and relatively weak cervical musculature. Victims of diffuse axonal injury are unresponsive or posturing at presentation and may have cranial nerve signs. ICP monitoring is indicated in those patients with a Glasgow Coma Scale score of 8 or less, although it is usually not elevated in diffuse axonal injury.^{52,53} Recovery after diffuse axonal injury is slow, protracted, and usually incomplete. Although not practical in the acute setting, outcomes research on MR abnormalities with techniques like diffusion tensor imaging and functional MR imaging is warranted.

The neurosurgical management of brain injury in children focuses on the preservation of function. Aside from injury prevention, the essence of treatment is the prevention or control of secondary injury to the brain that is precipitated by the initial trauma. The critical care management of TBI is discussed in Chapter 56. The cornerstone of the neurosurgical management of TBI is ICP control. ICP monitoring in infants and children differs from that in adults in both techniques used and thresholds for intervention. Normal ICP in children is not the same as in adults, and therefore lower ICP thresholds may be used, but it has yet to be studied whether more aggressive treatment thresholds positively affect outcome in children. The guidelines support a Level 3 option of using 20 mm Hg as the cutoff for treatment.² In infants and toddlers, techniques of ICP monitoring that require placement of a “bolt” or a threaded device secured in the skull may not be feasible. The thin skull of an infant or young child may not provide adequate purchase for the threads of the device to be secured in the skull; however, many widely used devices have alternatives for tunneling. The gold standard technique of ICP monitoring remains placement of a ventriculostomy catheter. External ventricular drains offer both ICP monitoring and the therapeutic option of CSF drainage. Continuous drainage, however, sacrifices real-time ICP monitoring and may be supplemented with a separate ICP monitor or the use of an external ventricular drain that is coupled with a fiberoptic monitor. Infection can be minimized with meticulous technique, diligent nursing care, and the use of an antibiotic-impregnated external ventricular catheter whenever possible.⁵⁴

Surgical procedures to control medically refractory elevated ICP should be tailored to the individual pathology and maximize cranial volume. Data suggest that decompressive craniectomy reduces ICP and may be useful for treating medically refractory elevations in ICP.^{55,56} Current guidelines list decompressive craniectomy with duraplasty as an option for patients with early signs of herniation or medically refractory intracranial hypertension.^{2,57} Although the type of procedure that works best is unclear (unilateral vs. bilateral craniectomy, duraplasty vs. no duraplasty), it appears that decompression procedures should be reserved for patients considered salvageable. This may include patients who deteriorate neurologically without a focal mass lesion and who have either unilateral or bilateral hemispheric swelling. This scenario of hemispheric swelling is exacerbated by impaired autoregulation and is not uncommon in infants after nonaccidental trauma.⁵⁸

53.3 Complications: Seizures

Seizures complicate head injuries in children at least as often as in adults, at a rate of approximately 5 to 12%, although younger children may be more susceptible.^{59,60} The incidence may be higher for those with the most severe TBIs.⁶¹ The vast majority of seizures after head injury are impact seizures, which occur within the first 24 hours after injury. Early posttraumatic seizures are associated with worse outcomes and greater severity of injury. Some observational studies have found seizure prophylaxis with antiepileptic drugs to be protective for early seizures but not for posttraumatic epilepsy.⁶²

53.4 Conclusion

TBIs are the most common cause of death in young people and therefore represent a significant public health problem and a medical challenge. Concussions, which are now recognized as a brain injury, may have significant cumulative sequelae, and effort should be made to protect the child with a concussion from further injury. The best treatment is prevention. It is hoped that injury awareness education programs like ThinkFirst (www.thinkfirst.org) and universal seat belt laws and helmet laws for children will reduce cases of TBI in our society. Advances in critical care medicine, cerebral monitoring, and the control of secondary brain injury will offer the greatest potential in the future to limit the consequences of TBIs. Neurosurgical intervention remains the cornerstone of treatment for TBIs, allowing the rapid identification and management of mass lesions, the control of secondary injury, and the monitoring and management of elevated ICP.

Pearls

- CT is a source of significant radiation exposure to children and is most useful in patients with altered mental status or behavior, scalp hematoma, loss of consciousness, severe mechanism of injury, evidence of skull fracture, or severe headache.
- Growing public awareness of concussion and perceived “minor” TBIs has been accompanied by a rise in ED visits for sports-related TBIs in the United States.
- Current guidelines list decompressive craniectomy with duraplasty as an option for patients with early signs of herniation or medically refractory intracranial hypertension.
- TBI is the most common cause of death in young people and therefore represents a significant public health problem and a medical challenge.

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54 Penetrating Craniocerebral Injuries

Ira E. Bowen, J. Gordon McComb, and Mark D. Krieger

Although not as common as closed head injuries, pediatric penetrating craniocerebral injuries (PCIs) account for significant morbidity and mortality within the pediatric population. Neurosurgeons are often presented with difficult management decisions when treating children with PCIs. Although many neurosurgical techniques and principles apply, several unique factors require further consideration. In this chapter, we summarize the current epidemiology, pathogenesis, diagnostic evaluation, and treatment measures available to the pediatric PCI population. Special attention is directed toward surgical management and the prevention and treatment of complications.

54.1 Epidemiology

Emergency neurosurgical admissions for pediatric PCIs are on the rise in the United States. A recent study reported a 138% increase in pediatric PCIs in the last decade, as well as a 4% rise in pediatric gunshot wounds to the head.¹ The true incidence is hard to quantify because of several factors, including the lack of a centralized database and the likelihood that victims incurring PCIs may die before reaching the emergency department (ED).² Additionally, many of these patients have been excluded from studies of head injuries, which tend to focus on closed head injuries. A study from Ontario, Canada, of all deaths from blunt or penetrating head injury in children younger than 16 years of age during the period from 2001 to 2003 found that only 12 of 234 deaths were caused by penetrating injuries.³ PCIs can be attributed to five overall causes: (1) accidental injury with sharp or semisharp objects, (2) warfare, (3) accidental discharge of firearms, (4) suicide, and (5) homicide.

In the pediatric population, PCIs can be attributed to countless random objects. Case reports have been written of PCIs caused by pencils and chopsticks,⁴ broom handles,⁵ metal strips, plant branches, kitchen knives, dinner forks, wires, nails, spikes, scissors, screwdrivers,⁶ and even a potato peeler.⁷ Often, flying debris during automobile accidents is a mechanism of PCI.⁸ Furthermore, low-velocity projectiles, such as arrows, BBs, and pellets discharged from pneumatic “toy” weapons, can be included in the category of causes of accidental injury.^{9,10} There are two key factors to consider in the management of impalements: first, penetration through thin calvarial regions is frequently associated with a high risk for vascular or cranial nerve damage, and second, retained foreign bodies (especially radiolucent objects) increase the risk for infection.

Throughout history, the pediatric population has been plagued by warfare, with countless injuries to both innocent children and young soldiers. Two Iranian series of traumatic aneurysms, detailing the effects of military PCIs on the pediatric population, reported that 25% of patients were 18 years of age or younger.^{11,12} Furthermore, a recent study of a field hospital in Iraq found 52% of pediatric consultations to be related to PCIs.¹³ It is of note, however, that unlike most civilian PCIs, those incurred during warfare are caused mainly by shrapnel rather than bullets, and when they are caused by bullets, the bullets tend to be high-velocity bullets associated with a much higher

mortality.¹⁴ Therefore, when the treatments and outcomes of PBI are studied, it is worth distinguishing between military and civilian populations. Because of the practical applications of this textbook, emphasis will be placed on civilian PCIs.

An alarmingly high number of PCIs in children can be attributed to the accidental discharge of firearms. Of all reported PCIs, 70% occur in the home setting.¹⁵ An increasing number of American households, 38% in a recent study, keep loaded weapons, allegedly for security reasons.¹⁶ However, in a series of 450 patients with PCIs from Cook County Hospital (Chicago, Illinois), only six firearm incidents were related to criminal invasion of a home.¹⁷ Furthermore, a study from the state of Washington stated that only 23% of firearm-related deaths were considered justifiable defensive homicides.¹⁸ Although it is less frequent in children, the practice of Russian roulette falls between the categories of accidental discharge and suicide, tending toward suicide,¹⁹ often resulting in lethal damage to the brain (► Fig. 54.1). More than 75% of the guns used in suicide attempts and in unintentional injuries of 0- to 19-year-olds were stored in the residence of the victim, a relative, or a friend.²⁰

Firearms continue to be a popular method for committing suicide, especially among men. Although the elderly remain the fastest-growing group affected by suicide,²¹ there has been a threefold increase in childhood suicide during the past 40 years.²²⁻²⁴ The exact reasons for these increases are unknown; however, the situation likely reflects an increase in violence, poverty, and the availability of weapons.²⁵ Suicide is currently the third leading cause of death in young Americans, with a rate of 13.1 per 100,000.²⁵ The most common means of suicide in American youth age 15 to 19 years is firearms, accounting for 736 deaths (3.4 per 100,000).²⁶ Hispanic women have the highest incidence of failed attempts, whereas rural Caucasian men have the highest completion rate.^{25,27-29}

Of concern are two societal factors, often interconnected, that are affecting children at an increasing rate. The growth of criminal activities surrounding the illicit drug culture and the growth of gangs in urban, suburban, and even rural

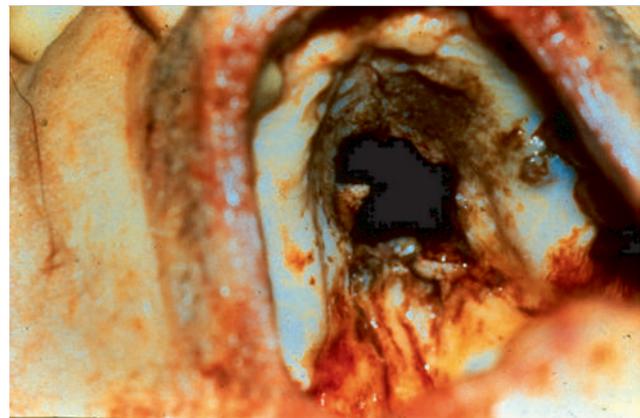


Fig. 54.1 Penetrating injury sustained during Russian roulette, with the bullet entering through the victim's palate.



Fig. 54.2 Photograph of gunshot injury and associated gang tattoo.

communities increasingly threaten the pediatric population (► Fig. 54.2 and ► Fig. 54.3).³⁰

Furthermore, the abundance and ready availability of powerful weapons being used with lethal intentions add to the toxicity of the situation. Homicide is the second leading cause of death in children in the United States after unintentional injuries, accounting for 11.4% of all deaths in 2011 and 12.1% of all deaths in 2010.³¹ The 8-year (1994 to 2002) homicide mortality rate per 100,000 persons was 26.4% for children aged 0 to 14 years.³² In 2009, firearms were involved in 84.5% of all homicides of people aged 15 to 19 years.²⁶ The fifth most common cause of death among patients aged 1 to 18 years reported in 2010 was firearm injury.³³ More than 11% of pediatric patients who were shot in 2011 did not survive.³⁴ In Tennessee, 47.8% of gunshot wound patients were between the ages of 14 and 25 years, whereas only 13.7% of the population of Tennessee falls within this age group.³⁵ In Harlem (New York City), a reported 40% of childhood gunshot victims were the intended targets, with 60% of their assailants children.³⁶ During 1991 in Los Angeles, California, 25% of all shooting victims, 412 of whom died, were younger than 18 years of age. Although traffic accidents are the leading cause of childhood deaths in the United States, gunshot homicides remain the leading cause of death among children in Los Angeles.³⁰

An exponential increase in gang-related activities can be seen throughout many areas of the country. The best data have been compiled in the city of Los Angeles. As of 2005, there were at least 1,108 identified gangs in Los Angeles County with 85,298 members, according to the CALGANG System of the California Department of Justice. Gang-related murders in Los Angeles increased from 271 in 1985 to 597 in 2001. In 1993, a study of 105 children treated for PCI at the LAC+USC Medical Center over an 8-year period found that 76% of the injuries were gang-related.³⁷ Likewise, Ordog et al³⁸ reported that 80% of the childhood victims in their series past the age of 10 years were involved in gang-related violence. Statistically, most shootings have involved African-American young men; however, homicides are in fact the second most frequent cause of death in girls of all ages.³⁹ Although gang-related and non-gang-related gunshot wounds show statistically significant differences in demographics and entrance sites, they do not differ in respect to survival and outcome.⁴⁰

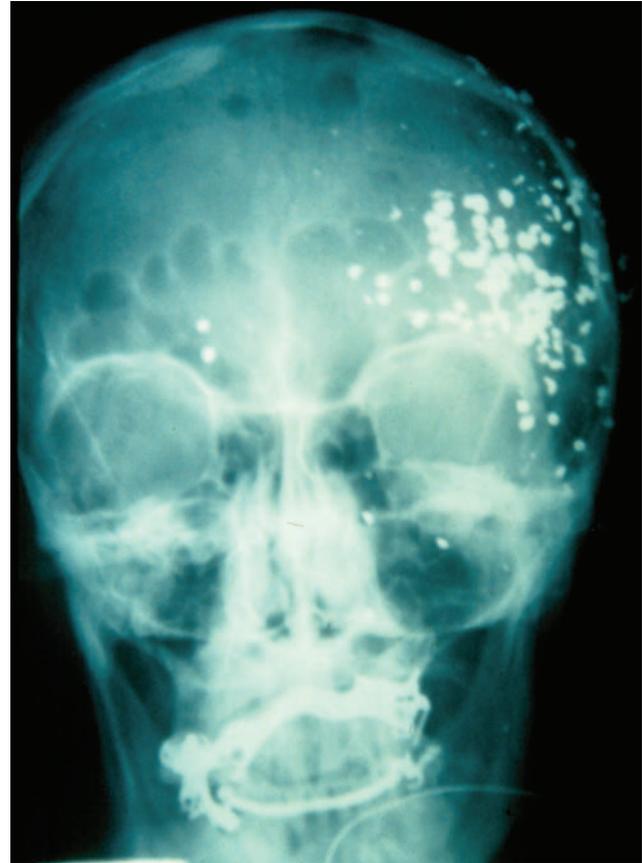


Fig. 54.3 Plain anteroposterior skull film of a 20-year-old man demonstrating diffuse extracranial and intracranial shrapnel. This resulted from a shotgun blast at approximately 20 ft.

While prevention of such devastating injuries is the overall goal, it seems drastic societal changes will be necessary to reverse the trend of gang-related childhood fatalities. In any case, neurosurgeons must be prepared to treat pediatric PCIs.

54.2 Clinical Presentation, Diagnostic Studies, and Early Treatment

The initial assessment and treatment of PCIs occur at the site of injury. An effective and expansive emergency medical system has been established in most communities in the United States; therefore, emergency medical technicians and paramedics generally provide initial care. Appropriate resuscitation and stabilization attempts combined with prompt transport to EDs have positively influenced outcomes.^{41,42} Through communication with initial emergency response teams, the neurosurgeon is often a participant in these activities and should be familiar with assessment and stabilization procedures at the early stages of treatment.

Immediate attention must be given to the fundamentals of airway, breathing, and circulation (ABCs). Furthermore, PCIs are not limited to the cranium and can often involve the face and

skull base. Obstruction of airways can be caused by blood, mucus, and posterior prolapse of the victim's tongue. Brainstem injury can cause alterations in breathing. If the patient's respiration is effective, an orally inserted airway protective device should be inserted under direct visualization. If ventilatory support is required, oral intubation should be performed. A short-acting, nondepolarizing neuromuscular blocking agent (e.g., vecuronium, 0.01 mg/kg every 15 to 30 minutes) and sedative agent (thiopental, 4 mg/kg, or midazolam, 0.07 mg/kg) may be administered to the semiconscious victim to minimize rises in intracranial pressure (ICP). Nasal intubation should be avoided because of the increased risks for raising ICP and for iatrogenic injury. Although the role of hyperventilation in acute management has not been clarified, the administration of 10 L of supplemental oxygen per minute at a rate of 24 breaths has been recommended.⁴³ Pulse oximetry and end-tidal carbon monoxide monitors are becoming standard equipment on ambulances and can be used to optimize patients' ventilatory status.

Despite the often dramatic appearance of PCIs, life-threatening hemorrhage is rare; local pressure is generally sufficient to control bleeding in the field. Saline-moistened gauze sponges should be used to cover wounds. Exposed impaling objects should be left intact. A rigid collar should be applied before transportation if the possibility of concurrent cervical injury exists. Although routinely carried by transport teams, corticosteroids are not beneficial. The acceptance of patients for interhospital transfer is another common situation encountered by neurosurgeons, especially those at regional trauma or referral centers. Although all of the above issues still apply, it is necessary to ascertain if nonneurosurgical injuries have been fully diagnosed and properly stabilized. Consultations with a general or trauma surgeon at one's home institution may be indicated; however, transfer should not be delayed to obtain diagnostic studies. Although availability has increased, it remains unclear if transport via helicopter or fixed-wing aircraft positively affects patient outcome.^{44,45} In fact, some studies indicate that the time for initial transport is inversely correlated with outcome, possibly because unstable patients with a worse prognosis are often transported more rapidly than stable ones.^{46,47}

Upon the patient's arrival at the neurosurgeon's institution, the first step is the collection and documentation of essential information. This includes vital signs, Glasgow Coma Scale (GCS) score, a basic general and neurologic examination with the patient fully unclothed to survey all body surfaces, and a description of visible injuries. The location, size, and appearance of all wounds should be recorded. Creating a photographic record is recommended.

Ongoing management of the airway and circulation is essential. Hypoventilation ($PCO_2 > 40$ mm Hg) and hypoxemia ($PO_2 < 80$ mm Hg) need be avoided, as well as excessive hyperventilation ($PCO_2 < 25$ mm Hg), which can adversely affect cerebral blood flow. An orogastric tube should be placed to decompress the stomach. A euvolemic state can be maintained by the judicious use of isotonic crystalloid fluids (normal saline) titrated to urinary output, accurately measured via a Foley catheter. Hemoglobin and hematocrit should be determined and type- and cross-matched blood obtained. An extremely low hematocrit can be caused by massive hemodilution via resuscitative efforts or by large blood loss, the latter resulting either from a laceration of a major vessel or from internal or external hemorrhage

at other locations. This can lead to sudden and unheralded cardiovascular collapse, mandating aggressive correction of hypovolemia and anemia. In the young infant, enough blood can be sequestered in the scalp or cranial vault to result in hypovolemic shock without obvious external blood loss. Insertion of a central venous catheter is indicated for the assessment of intravascular volume status in the hemorrhaging patient.

The management of raised ICP or lowered cerebral perfusion pressure (CPP) may be necessary, either empirically in patients with deteriorating neurologic status or objectively in patients with intracranial monitors in place. Although potentially lifesaving in a herniating patient, the effect of such management on outcome beyond the initial resuscitative period is yet to be fully established. Some adult studies report improved outcome when the blood pressure and ICP can be controlled to ensure a CPP above 70 mm Hg^{48,49} however, pediatric studies replicating these results are lacking. Pediatric studies have established a correlation between CPP below 40 mm Hg in patients younger than 10 years and high mortality rates.^{50,51} Appropriate measures may include mannitol (0.5 to 1 g/kg intravenously every 2 to 4 hours to a maximum serum osmolality of 310 mOsm/L), furosemide (0.5 to 1 g/kg every 1 to 2 hours), and boluses of 3% NaCl (2 to 5 mL/kg initially followed by 2 mL/kg every 6 hours) and pressor agents, such as dobutamine. Elevation of the patient's head may slow hemorrhage from wounds but may adversely lower the CPP.⁴³

Disseminated intravascular coagulation (DIC) can occur any time after significant cerebral injury as a consequence of the release of brain tissue thromboplastin and initiation of the coagulation/thrombolytic cascade. It is directly correlated with the amount of brain injury and likely happens as frequently in the pediatric population as in adults. The prothrombin time, partial thromboplastin time, level of fibrin degradation products, and platelet count should be followed serially to identify this form of consumptive coagulopathy. The replacement of appropriate blood components (fresh frozen plasma, cryoprecipitate, platelets) should be initiated to prevent uncontrollable hemorrhaging. Furthermore, DIC indicates a poor prognosis in the adult population⁵² and may be a similarly ominous sign for infants, having been shown to be a predicting factor in the Glasgow Outcome Scale score⁵³ and associated with poor outcome.⁵⁴

54.3 Diagnostic Imaging

Computed tomography (CT) of the head is strongly recommended to evaluate the patient with PCI.⁵⁵ In addition to axial views of bone and soft tissue, coronal sections may be useful in patients with skull base or high convexity involvement. In selected cases, plain films may help to delineate skull fractures and bullet fragments; however, the CT scout alone is generally sufficient (► Fig. 54.4). Routine magnetic resonance (MR) imaging is not generally recommended in the early evaluation period.⁵⁵ Serial 5-mm CT cuts should be obtained from the vertex to the foramen magnum, with windowing to image bone, blood, and brain. Rescanning at different gantry angles can be helpful if large metallic fragments create markedly distorted images.

Subgaleal hematomas, common among children with PCIs, may be responsible for a significant loss of circulating blood volume. Skull fracture patterns can be used to distinguish entry



Fig. 54.4 Axial computed tomographic scan showing extensive cerebral damage from the bullet.

and exit wounds and the paths of projectiles. Entry sites are characterized by small holes, in-driven fragments, and beveled edges; exit wounds tend to be larger and irregular. The paranasal sinus should be studied for the presence of air–fluid levels. Although extradural hematomas are rare in PCIs, their rapid identification and surgical removal offer improved survival rates compared with those of subdural hematomas and subarachnoid hemorrhages commonly associated with PCIs. On CT scans, cerebral contusions and parenchymal hematomas may appear bright, dark, or of mixed density based on the proportions of hemorrhage and edema. Isodense contusions occur with some frequency and are better imaged with MR imaging, if necessary. Potential findings also include intraventricular blood, shear injury (e.g., blood or edema along the corpus

callosum), obliteration of the basal cisterns, and loss of gyral patterns.

Follow-up CT is warranted in selected cases because of the possible delayed development of intracranial hematomas. One study reported the highest rate of intracranial hematomas at 3 to 8 hours after initial injury. The development of a hematoma or further cerebral edema can present as acute deterioration, and therapeutic intervention may be required. Ischemic injuries, such as bilateral hippocampal, cerebellar, or watershed distribution infarction, may be seen on later scans.

MR imaging may play a role in evaluating injuries in several situations. First, it may be useful to ascertain cerebral contusion and shear injuries in patients whose neurologic examination is worse than would be predicted by CT scans. Second, MR angiography may be used to screen for traumatic aneurysms; however, in many cases in which vascular injury is suspected, conventional cerebral angiography is recommended. CT angiography may be beneficial as well. Third, gadolinium-enhanced MR imaging is more effective than contrast-enhanced CT when it comes to detecting cerebritis or the early development of extra- or intracranial abscesses, and it may be indicated in the evaluation of the febrile patient. Last, MR imaging may be useful in evaluating injuries from penetrating wooden or other nonmagnetic objects.⁵⁵

Although MR imaging can be done safely in the majority of cases with retained metallic objects, neurosurgeons must exercise caution when ordering images. An *in vitro* and clinical study revealed that most bullets produced in the United States and shotgun pellets used in domestic and police situations are nonferromagnetic and can be exposed to contemporary MR imaging magnets (1.5-tesla range) without risk for rotational injury.⁵⁶ Another recent study has indicated that common, commercially available bullets manufactured in the United States are safe in MR imaging scanners up to 7 tesla; however, armor-piercing rounds with steel cores are not.⁵⁷ Additionally, a study focused on fragments resulting from combat and terrorist attacks found these artifacts to be safe at 1.5 tesla.⁵⁸ ▶ Table 54.1 summarizes the ferromagnetic properties illustrated in these studies. Almost all metallic objects will distort and degrade images and can reduce the diagnostic yield of a study. As

Table 54.1 Summary of the literature on the potential for rotational movement and image artifacts of metallic objects with magnetic resonance imaging

Object	Composition	Movement potential	Artifact potential ^a
Shrapnel (bombs and artillery shells) or zip gun	Steel, lead, or mixed	++ to +++	0 to +++
Bullets	Bronze projectile	0	+ to +++
	Lead projectile	0	++++
	Lead projectile; steel- or copper-jacketed	++	+++
	Steel core; copper-plated, steel-jacketed	++	+++
Shotgun ammunition	Lead shot	0	+
	Steel shot	+	+
Pneumatic gun ammunition/BBs	Steel pellets	+	+

Source: From Eshed et al,⁵⁸ Zheutlin et al,⁵⁹ and Kim and Zee.⁶⁰

^aArtifact potential rated from 0 (least) to ++++ (most).

described in the ophthalmology literature, and of particular relevance to the pediatric neurosurgeon, BBs and pellets fired from many pneumatic weapons are generally made of steel and have the potential to move in strong magnetic fields.⁵⁹ The best approach is to have an expert, such as a police officer, examine the weapon, spent casings, unfired ammunition, or any relevant evidence retrieved from the patient to determine the composition of the projectile. If the composition of the projectile cannot be confirmed, the neurosurgeon must weigh the benefits of MR imaging against the potential for injury to neural or vascular structures if the object moves during imaging.

Although useful, prognostication based on radiographic imaging is imprecise. Without an initial GCS score, no single radiographic finding can be independently predictive of outcome.⁶⁰ Still, several observations have been noted, including elevated mortality rates with multiple-lobe,⁶¹ bihemispheric,^{62,63} multipolar,⁶⁴ and transventricular injuries^{62,64,65} (► Fig. 54.5), as well as subarachnoid hemorrhage,^{66,67} intraventricular hemorrhage,⁶⁸ intracerebral hematomas,⁶² and basal cistern effacement.⁶⁹ Furthermore, poor outcome associated with bihemispheric injuries has been reported in two groups, and occipital entrance wounds are usually fatal.^{70,71}

54.4 Surgical Treatment

Although most neurosurgeons would decline to operate on a patient without neurologic function, the choice for surgical intervention can be complex. When a low GCS score^{4,72,73} is combined with an ominous sign, such as nonreactive pupils or refractory hypotension, the decision to withhold surgery seems warranted.⁷⁴ Upon review of the neurosurgical literature, the benefit of operating on patients with post-resuscitative GCS scores of 3 to 5 at the time of presentation remains unclear because of a mortality rate higher than 80% and a rate of poor outcomes that approaches 100%, with significant yet infrequent exceptions.⁷⁵ The issue becomes more complex in the pediatric population because predictive pediatric models are nonexistent. Furthermore, the emotional overlay of tragedy is often compounded when children are involved, putting an overwhelming burden on parents when it comes to decision

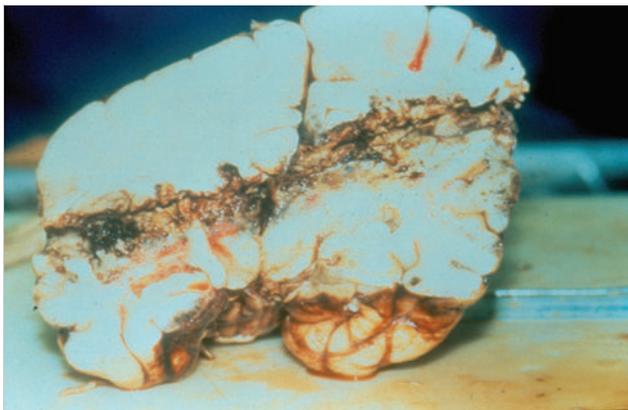


Fig. 54.5 Autopsy brain specimen of a through-and-through penetrating cerebrocranial injury with ventricular compromise following discharge of a rifle at short range. Note the discoloration of the tract and multiple areas of cavitation.

making. Under these circumstances, decisions must be individualized and based on an analysis of the clinical and radiologic factors, as well as discussion with colleagues and family members. In light of these complexities, neurosurgeons should generally err on the side of aggressive treatment with pediatric patients who have PCIs.

Kaufman⁷⁴ has suggested three primary reasons to operate: (1) to remove foreign objects (e.g., missile fragments, bone) to prevent secondary complications, such as infection, posttraumatic aneurysms, and seizures; (2) to remove necrotic brain to prevent further hemorrhage, edema, and scar formation; and (3) to eliminate mass effect, especially that associated with hematomas, on viable brain. Other indications for operative management include debridement and closure of scalp wounds, repair of vascular injuries, and placement of a device to monitor ICP. Unfortunately, the data are insufficient to show the impact of these procedures on clinical outcome with accuracy. In any case, the current understanding of traumatic pathophysiology and standard of care would suggest that such procedures are often appropriate.⁷⁶

Certain issues warrant further discussion. First, the timing of surgery is an important consideration. Certainly, hemodynamically unstable, multiply traumatized patients and those with DIC must be stabilized to avoid high operative morbidity and mortality rates. Although early and aggressive debridement has been the standard treatment in military PCIs,^{77,78} prompt but locally confined debridement is considered sufficient in civilian PCIs.^{74,79} For patients presenting more than 24 hours after injury, more aggressive debridement would be indicated because of an increased risk for infection. Scalp and skull wounds should always be explored for necrotic skin, hair, and bone fragments that can be safely removed. Dural and vascular injuries should be repaired and copiously irrigated. No evidence indicates that extensive parenchymal debridement or the removal of deeply penetrating bullet fragments or bone prevents infection. Two studies suggest that retained fragments may increase the incidence of late seizure development and traumatic aneurysm formation^{11,12}; however, this must be weighed against the risk for further neurologic injury during operative manipulation. Most neurosurgeons recommend the prompt removal of “significant” hematomas; however, the minimal volume has not been established.⁷⁴ Despite recommendations for a more aggressive approach with posterior fossa wounds, because of the small volume of this compartment and poor tolerance of compression, two series have found that pediatric patients with occipital entry wounds have poor outcomes despite surgical intervention.^{70,71}

In most cases, standard craniotomy techniques should be applied. An important consideration in the design of the scalp flap is the excision of contaminated and heavily damaged soft tissue. Bone from the scalp and entrance sites can be removed if small local debridement is anticipated. Although some authors have advocated osteoplastic flaps, no reduction of the infection rate has been shown with this technique.^{52,80} Debridement of the parenchyma should be performed with the use of copious isotonic fluid irrigation and controlled suction. The primary goals are to remove large, easily accessible foreign objects at the entry and exit sites, remove hematomas, and control hemorrhage. The insertion of small-diameter red rubber catheters followed by irrigation to assist with the removal of deeper hematomas is

rarely warranted. If necessary, a hemostatic agent such as peroxide or oxidized regenerated cellulose can be employed. Intraoperative ultrasound can be effective in localizing bone, metal, and clots. Objects as small as 1 mm have been detected when a 7.5-Hz probe was used. (However, deeply embedded objects should probably be left in place, regardless of size.⁷⁴) Repair of a transgressed dural venous sinus is indicated if there is active hemorrhage, but the bleeding can often be controlled with tamponade. The anterior sagittal sinus may be ligated as far posteriorly as the entrance of the first major cortical vein.

The dura mater may be closed primarily or reapproximated. One recent military series reported a reduction in the incidence of cerebrospinal fluid (CSF) leaks and infectious complications with dural closure⁸¹; another study stressed watertight closure of wounds (with a graft if necessary) and closure of the scalp in layers.⁷⁷ In general, if the wound can be debrided and irrigated and the scalp can be closed to prevent external leakage of CSF, then a dura mater approximation with absorbable suture material should be sufficient. The application of fibrin glue to the suture line can be considered because it is safely used in non-trauma situations to effectively prevent CSF leaks.⁵² When large defects are closed, suitable dural substitutes include vascularized pericranium, temporalis fascia, and fascia lata, although one author found that the latter did not prevent infection.⁸² Silastic (Dow Corning, Midland, MI) and other nonabsorbable materials should be avoided because they have been implicated in infections and remote hemorrhages.⁸³ In many cases, dural defects can be managed with the application of a large piece of gelatin film between the exposed dural edges and the cortical surface plus the placement of oxidized cellulose on the external surface of the exposed dura mater.

Cleansed bone should be replaced unless highly contaminated. Although wire mesh can be safely used, acrylics should be avoided because of their tendency to harbor bacteria in their porous matrix. In one series of patients undergoing elective cranioplasty with methylmethacrylate, 22% developed infections if the mucosa of the frontal sinus was exposed.⁸⁴ A delay of 6 to 12 months has been recommended if an extensive cranioplasty is required.⁷⁵

If possible, the scalp should be closed in two layers, with absorbable sutures approximating the galea and a second suture line to appose the skin edges. A rotational flap may be necessary in cases of large defects. The prophylactic insertion of a lumbar drain to promote sealing of dural tears is not indicated; however, this method may be employed if a CSF leak develops.

The risk for infection and CSF leak is increased in patients who sustain transorofacial wounds, and thus special consideration is necessary.⁷⁴ The assistance of plastic, head and neck, and/or oral surgeons may be warranted. Aggressive debridement of all cavities communicating with the intracranial compartment, exenteration of the frontal sinus mucosa, and dural repair are the standard treatments. Also of importance in these cases is perioperative broad-spectrum antibiotic coverage for gram-positive, gram-negative, and anaerobic organisms.

The insertion of an ICP monitor at the time of operation should be considered, based on the extent of the injury. Delayed edema occurs regularly in patients with PCIs, and rapid increases in the ICP may indicate the onset of progressive cerebral edema, hydrocephalus, or hematoma formation. Although ICP monitoring is indicated for all patients with severe closed head

injuries,^{41,42} fewer than half of surveyed neurosurgeons reported routinely monitoring the ICP of patients with severe PCIs.⁸⁵ Ventriculostomies can provide an advantage over extraventricular monitoring systems by allowing CSF drainage for the management of increased ICP or impaired CSF circulation. The efficacy of measures to lower the ICP in both adult and pediatric PCI victims is yet to be determined.

54.5 Complications

54.5.1 Infections

The specific rate of extracranial and intracranial infections in children with PCIs has not been reported; however, broader studies have shown high infection rates ranging from 25 to 50%.^{86,87} Some of the possible infectious complications include scalp cellulitis and abscess formation, osteomyelitis, epidural and subdural empyemas, meningitis, ventriculitis, cerebritis, and brain abscess. Based on studies of the general population, several factors are apparent when infectious complications are treated. First, the speed of the penetrating object is important. Although generally seen in a military setting, PCIs from high-velocity bullets tend to have a lower rate of infection, in the range of 5 to 7%.^{77,79,80,82,85,88-90} A study of low-velocity injuries in a pediatric population showed an alarmingly high rate (43%) of infectious complications.⁶ In the report of 54 cases, 14 patients developed brain abscesses, 6 meningitis, 2 scalp infections, and 1 calvarial osteitis. In almost all of the cases, infection was caused by *Staphylococcus aureus*. Second, there is a positive correlation between the infection rate and the level of contamination as well as delay in treatment. In-driven hair, scalp, and superficial bone in volumes larger than 1 mL are significant risk factors for infectious complications.^{89,91} Third, concomitant injuries (e.g., skull fractures with CSF leakage, paranasal sinus fractures that communicate intracranially, and oral injuries) have been historically associated with increased infectious complications. Fourth, the composition of the penetrating object correlates with infection rates, especially in instances in which foreign material is retained. Although most bullet fragments are hot, inert metals, many organic materials, especially wood, can harbor many pathogenic microorganisms. In a study of 42 patients (80% of them pediatric patients), almost 50% developed an infectious complication.⁸⁷ Finally, surgical exploration and debridement play an important role in infectious complications. Although the removal of gross superficial contamination is important, the removal of deeply embedded bone and projectile fragments does not decrease the incidence of infection. Several authors reported good results with little or no retrieval of foreign objects.^{63,88,92} Some recommend serial CT if a minimalist surgical approach has been taken; however, careful clinical surveillance is generally sufficient on a long-term basis.

Prophylactic antibiotics do not ensure the avoidance of infection, nor has the role of prophylaxis been fully clarified. Many authors support the need for the early administration of broad-spectrum antibiotics^{65,68,93} however, others recommend that intraoperative cultures be obtained and that antibiotics be administered only when the cultures are positive. One study reported a 10% incidence of meningitis and wound infection despite the use of antibiotic coverage.⁹⁴ A variety of appropriate antibiotics are available; these range from single, semiselective

agents like cefazolin to third-generation cephalosporins plus antipseudomonal and anaerobic agents. Antimicrobial therapy is given intravenously for 5 to 14 days with or without additional oral agents for a similar period. To reduce the rate of bacterial resistance as well as cost, the nature of the contamination should be considered when an antibiotic is chosen. We recommend that a 7- to 10-day course of cefazolin be administered to minimally contaminated patients, and that a 7- to 14-day course of ampicillin, gentamicin (or third-generation cephalosporin), and metronidazole be given to heavily contaminated patients. In the presence of methicillin-resistant *S. aureus*, vancomycin should be used instead of ampicillin. Furthermore, the debridement site should be cultured intraoperatively, as one study found a 76% correlation between wound cultures and brain abscesses in patients in whom this complication developed.⁹¹

Evaluation for infection should definitely be undertaken in the case of patients with PCIs who have fever, a change in mental status, or new focal neurologic deficits. Although laboratory studies, such as white blood cell count, C-reactive protein, and erythrocyte sedimentation rate, can be correlative, obtaining an imaging study is a priority. CT offers the benefits of speed and affordability, but contrast MR imaging may have better diagnostic abilities. MR imaging can discern soft tissue, bone, and brain infections in their earliest stages. T1-weighted images will show sulcal effacement with mass effect, whereas T2-weighted images show increased signal of cerebral edema associated with early cerebritis.⁹⁵ It should be noted that during attempts to distinguish between an infectious process and simple posttraumatic cytotoxic edema, paramagnetic contrast enhancement will generally be present in developing cerebritis and abscesses, although exceptions have been found early in the process.⁹⁶ When imaging is ambiguous, empiric antibiotic coverage should be considered and a study repeated 7 to 10 days later to determine if a characteristic ring-enhancing lesion has developed. In patients with meningitis, fine-cut CT, CT cisternography, or MR imaging of the skull base can help evaluate potential sites of CSF leakage. Appropriate medical and/or surgical intervention should be undertaken as directed by the imaging and is discussed elsewhere.

54.5.2 Seizures

Cases of seizure, including early-onset seizure (less than a week), late-onset seizure (after a week), and epilepsy (chronic seizure disorder), are not well documented in children with PCIs. If one considers the nature of the central nervous system in pediatric patients with closed head injuries, which has been studied, one would expect the rate of seizures to be high after PCIs.⁹⁷ In series of adults with PCIs, the incidence of early seizures ranged from 1 to more than 30%, considerably higher than the incidence in patients with closed head trauma, and the incidence of late seizures has been reported to be as high as 54%.⁹⁸ In most cases, late seizures occur four to eight times more often than early seizures, implying that the two conditions may have a different pathogenesis.⁹⁶ The data, however, are confounded by the variable administration of prophylactic anticonvulsant medications.^{63,93,97-99}

To better understand the incidence of seizures in the pediatric population with PCIs, it is necessary to evaluate the literature on traumatic brain injury that is restricted to this age group. Despite the fact that the vast majority of patients sustained closed head injuries, several studies have reported incidence rates of early seizures of 5 to 15%.¹⁰⁰⁻¹⁰⁹ One series of patients with low-velocity PCIs reported a 17% incidence of early seizures.⁶ The long-term follow-up of pediatric patients with PCIs is poor; likewise, the incidence rates of late seizures and epilepsy have been reported infrequently. However, larger series with small numbers of children suggest that late seizures and epilepsy are more frequent than early seizures.

Some authors have attempted to identify the clinical characteristics that are predictive of posttraumatic seizures in children following PCI.¹⁰³⁻¹⁰⁶ Possible predictors include a GCS score of 3 to 8, diffuse cerebral edema, acute subdural hematoma, prolonged loss of consciousness, and depressed skull fracture. The strongest indicator is a persistently low GCS score, with up to 53% of children in this category manifesting early seizures. However, in one retrospective analysis of seven children with PCI and a low GCS score, none manifested early seizure activity.¹⁰⁶ Overall, the identification of predictive factors for posttraumatic seizures in the pediatric population remains incomplete.

Although earlier literature suggested no benefit,¹⁰⁷⁻¹¹⁰ prospective and retrospective studies including both adults and children generally affirm the efficacy of phenytoin for the prevention of seizures in the first week after injury.^{98,102,106,111,112} In one survey, 84% of neurosurgeons reported the routine use of prophylactic anticonvulsant medication for patients with severe head injuries.⁸⁴ In a prospective adult trial, the reduction in the rate of seizures was nearly fourfold, from 14% in the placebo group to 4% in the treated group. Still, in studies, the rates of late seizures and epilepsy have not been reduced, suggesting that prophylaxis is not effective on a long-term basis.

Overall, based on a summary of the literature, prophylactic anticonvulsants in the first week after injury would be recommended for most pediatric patients with PCIs. Seizure-related increases in ICP and other secondary injuries may then be reduced. Withholding prophylactic anticonvulsant medications from children with minor injuries and high GCS scores would also be an acceptable protocol. After the first week of hospitalization, the decision to continue anticonvulsants should be made on an individual basis. However, the occurrence of early seizures does not bode well for patients, who remain at high risk for the development of epilepsy requiring long-term anticonvulsant medications.¹⁰¹

Although phenytoin is the most commonly used anticonvulsant medication in published series, other medications should be considered. Phenytoin, when administered orally or intravenously, is highly effective and generally safe. For very young children, or those who may need extended therapy, phenobarbital is a good choice; however, it can cause adverse behavioral changes. During the acute period, intravenous administration is crucial, especially in the case of infants, who have poor enteral absorption of many anticonvulsant medications. If intravenous access is not possible, the rectal route is acceptable for phenytoin and the benzodiazepines; hospital pharmacies can generally

prepare the medications quickly if needed. The key factors in safety and effectiveness are administration of the loading dose and surveillance with frequent serum levels. Assessment of the levels is necessary every 2 to 3 days, especially because significant fluctuations in phenytoin levels are observed in severely injured patients with unstable serum protein levels.¹¹³

Discontinuation may be possible after 3 to 6 months if the patient remains seizure-free; however, little guidance has been found in the literature regarding this matter. If seizures have developed in a child more than a week after injury, anticonvulsant medication should be continued for at least 2 years, at which point the recurrence rate is still expected to be high. Furthermore, over time, the clinical and electroencephalographic (EEG) manifestations may change, with one study showing an evolution from early generalized to later focal types based on the site of injury.⁹⁷ The treatment of focal seizures, which can be difficult to control, may require the help of a pediatric neurologist. Before anticonvulsant medications are withdrawn, an EEG is often sensible.

54.5.3 Traumatic Aneurysm Formation

The formation of cerebral aneurysms after PCIs is an uncommon yet well-known event, occurring in up to 5% of patients with PCIs in all age groups.^{11,12} Although the incidence in pediatric PCIs is unknown, some suggest it is more common among the pediatric population than in adults.¹¹⁴ A study at Children's Hospital Los Angeles found 7 cases of pediatric traumatic aneurysm over a 17-year period, one of which was secondary to PCI.¹¹⁴ In a military series from Lebanon, 13 of 40 victims in whom aneurysms developed after injury to the head from high-velocity projectiles were 18 years of age or younger.^{11,12} Low-velocity injuries can also cause aneurysms, as shown in a study of 54 patients, 2 of whom developed traumatic aneurysms after impalement or pellet wounds.⁶

Pseudoaneurysms are the most common lesions and are thought to result from damage of the arterial adventitia and media within hours or a few days after injury. Pseudoaneurysms can evolve along the length of any damaged cerebral artery, including the intracavernous carotid, can involute or enlarge unpredictably, and may hemorrhage early or many years later, with potentially devastating outcomes. Behavioral and neurologic changes have been linked to these lesions.¹¹⁴ Acknowledged predictors for the development of traumatic aneurysms include: (1) course of a projectile or bone fragment through areas of dense vasculature or the skull base, (2) impalement of an object through the above-mentioned regions, (3) trans-hemispheric passage of a projectile, (4) large intracerebral hematomas associated with an entrance wound, (5) multiple fragments with scattered paths, and (6) heavy arterial bleeding during initial debridement.^{11,12,67} Cerebral angiography at 7 to 10 days after injury should be seriously considered in the presence of any of the above-mentioned factors. Because immediate surgical treatment is considered safe and effectively eliminates the risk for hemorrhage, aneurysms of any size should be clipped, excised, or wrapped. Similarly, abnormal vessels should be treated at the time of initial debridement.

54.5.4 Wandering Fragments and Lead Poisoning

Several case reports exist of wandering metallic fragments along the neuraxis. Reports have been made of the migration of shotgun and air rifle pellets into the anterior and posterior cerebral circulation through both intra- and extracranial wounds, creating cerebral infarctions.¹¹⁵ One author describes cerebral softening, leading to the migration of large bullet fragments. The high specific gravity of metal compared with that of brain, and the sink action of the CSF flowing through the cerebral ventricles, may contribute to this condition.¹¹⁶ Both fatal migration into the brainstem and the development of hydrocephalus when fragments occlude the cerebral aqueduct have been documented.¹¹⁷⁻¹¹⁹

Another uncommon complication of retained metal fragments is lead poisoning.¹²⁰ Several weaknesses in the analysis of the data for this topic have been reviewed.¹²⁰ Well-documented cases exist of victims with an extensive amount of shotgun pellet throughout the body. Unfortunately, urine lead levels may be unreliable. Furthermore, the latent period of lead poisoning can vary from 6 months to many years, and the signs and symptoms are generally erratic and indistinct, including weakness, dizziness, headache, abdominal pain, constipation, and vomiting. Because of the decline in the use of lead in ammunition, the already infrequent problem of lead poisoning should wane even further.

Considering the above factors, if surgical removal is contraindicated because of potentially worsening neurologic injury, retained fragments near ventricles or major cerebral vessels should receive diligent surveillance. An immediate radiographic evaluation (either CT or cerebral angiography) should be undertaken at the onset of focal deficits or a deterioration in clinical status. Because of the potential for secondary hydrocephalus or neurologic injury, most intraventricular fragments should be removed. Locating the object radiographically in the operating room, before surgical exposure, is recommended because large bullets can move with positioning.¹¹⁶ When there are large amounts of retained lead fragments, the patient should be monitored clinically for signs or symptoms of lead poisoning. In the case of diagnostic evaluation and/or chelation, consultation with a hematologist or toxicologist is recommended.

54.6 Survival and Prognostic Factors

Any discussion of outcomes in children with PCIs is plagued by problems that include early and high mortality rates compounded by the overall small number of victims, so that predictive analysis is difficult. As mentioned earlier, withholding care from a patient presenting with a GCS of 3 and fixed pupils after initial resuscitative efforts seems wise. Likewise, one series¹²¹ noted that no pediatric patient with a traumatic brain injury and concomitant protracted anoxic insult regained useful consciousness, suggesting that supportive care alone is appropriate in this group. Aggressive neurosurgical management should be

pursued in patients with GCS scores of 12 to 15 and limited parenchymal injuries because they often have excellent functional recoveries.

The dilemma most commonly associated with PCIs is the management of patients with moderate to severe injuries. Many seriously injured children can survive with aggressive surgery; however, quality of life is often greatly compromised. One series of patients presenting with GCS scores of 3 to 5 reported that 99% of nonaggressively treated patients died. Although the majority of patients who underwent surgery survived, 90% had severe long-term disabilities, with families and physicians often questioning the good of the intervention.¹²² Other series report a multitude of lasting complications, including persistent vegetative state, functional dependency, blindness, paralysis, seizure disorder, and profound neuropsychological alterations affecting memory, language, and behavior.^{71,123,124} An analysis of war veterans who were young adults at the time they sustained PCIs found a substantial decrease in life expectancy correlated with posttraumatic seizure disorder in comparison with the general population.¹²⁵

Most studies of children with craniocerebral trauma focus on those with closed head injuries, and one must be careful when applying their findings to children with PCIs. Regardless, studies of outcome in children with severe craniocerebral trauma create a disconcerting image. One study found that long-term survival is much more common in children with prolonged periods of unconsciousness or vegetative state than in adults.¹²¹ At least one study has connected GCS score with neurobehavioral outcome, showing that patients with an initial score of 5 or less, as well as those who had a slow improvement in their GCS score, demonstrated substantial long-term impairments in intellect, adaptive problem solving, memory, academic performance, motor performance, and psychomotor problem solving.¹²⁶ Still, even children with less severe injuries have been found to have significant limitations in physical health and behavioral problems and can require special educational intervention in comparison with the general pediatric population. Contrary to the belief that children fare better than adults, the analysis of Kaufman et al¹²³ of a small group of patients with PCIs found similar incidences of problems regardless of age, including functional disability, need for special education, and extreme emotional lability. Generally, if improvement occurs in moderately or severely injured children, it usually plateaus after the first year following injury.^{121–127} In some children with less severe injuries, the harmful consequences for cognition, behavior, and psychosocial adjustment may not be fully realized until adulthood.^{128,129} One study found that only 23% of adults who sustained traumatic brain injury in their preschool years were able to work, and only 36% lived independently in the home setting.¹²⁹ Another study of PCIs, focusing on patients presenting with GCS scores of 3 to 8, concluded that although mortality rates are high, patients who survive to receive inpatient rehabilitation can achieve functional improvement.¹²⁷ Long-term focal deficits can often be reliably predicted based on the location of an injury,¹³⁰ but the heterogeneity of the PCI population makes further predictions and analysis quite challenging.

Pearls

- Early involvement by the neurosurgeon in the initial assessment and management is essential for timely and appropriate decision making. Children presenting with GCS scores of 3 to 4 or with posterior fossa entrance sites are likely to die and should be managed accordingly.
- Surgical intervention should be individualized according to the site and extent of injury. Limited debridement and careful wound closure are often sufficient. Further evaluation (e.g., angiography) and deeper exploration may be indicated when large foreign bodies are in juxtaposition with the ventricles or major cerebral vessels.
- Short courses of prophylactic antibiotics are generally indicated, especially in patients with low-velocity injuries, which have a high risk for infectious complications.
- Prophylactic anticonvulsant medications are generally indicated during the first week after injury. Beyond that period, the neurosurgeon should use discretion about prolonged administration, realizing that the prevention of late seizure activity has never been demonstrated. The development of late seizures, however, generally heralds the onset of a chronic seizure disorder that will require long-term anticonvulsant medication.
- The neurosurgeon should remain vigilant for the development of delayed complications. These include brain abscess and traumatic aneurysm formation, wandering intracranial fragments, and lead poisoning.
- Residual and delayed neurologic and functional deficits are common, even though considerable improvement may be observed in the first year after injury.

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55 Intracranial and Extracranial Hematomas in Children

Anthony Figaji

There are many causes of intracranial and extracranial hematomas in children; this chapter focuses on the most common and the most relevant to neurosurgical intervention.

55.1 Basic Pathologic and Pathophysiologic Considerations

Intracranial hematomas present a major risk for death and disability because they increase intracranial pressure (ICP) and displace brain. The volume within the cranial compartment is fixed (Monro-Kellie hypothesis); therefore, any increase in one of the principal components (brain, blood, cerebrospinal fluid [CSF]), or the addition of another component (e.g., hematoma) must be compensated for by a change in one of the other components—initially, CSF and venous blood. If this compensation is inadequate or exhausted, ICP increases and brain shift occurs, leading to global or focal ischemia, brain distortion, focal deficits, and decreased consciousness. Of great clinical importance is the nonlinear relationship between increased intracranial volume and pressure. When the brain is able to compensate for changes in volume, there is little change in ICP; however, once the compensatory capacity, or compliance, of the intracranial space is exhausted, ICP increases dramatically with any further small increase in volume. Therefore, an awake patient with an intracranial hematoma remains at risk for sudden deterioration and should be treated with caution and care, even when he or she is neurologically intact. Open fontanels and sutures in infants and young children offer limited protection against an acute rise in pressure.

The risk for an intracranial hematoma depends on the etiology, location, speed of accumulation, and eventual size. Hematomas of arterial origin accumulate most rapidly. Posterior fossa hematomas are particularly dangerous because of the relatively contained infratentorial space, resultant pressure against the brainstem, and occlusion of the fourth ventricle leading to hydrocephalus. The condition of the brain is important—large intraparenchymal contusions and/or brain swelling may lower the threshold for removing relatively small extra-axial hematomas. Conversely, if a lesion has minimal mass effect in a patient who is systemically unstable (e.g., a patient with polytrauma), is medically unwell (e.g., a patient with cardiac disease), or has a coagulopathy, an initial conservative approach may be more prudent. Acute evaluation must also consider the potential dynamic element; very early imaging may underestimate the enlarging hematoma, and the initial clinical examination must be supported by ongoing and close neurologic monitoring to detect any delayed deterioration in a timely manner.

55.2 Imaging

Plain skull radiographs rarely contribute to the initial assessment; although linear fractures may indicate an underlying hematoma, clinically important intracranial pathology in trauma may be present with no fracture, and therefore plain skull

radiographs are not reliable indicators for further imaging. The exceptions are suspected nonaccidental injury and the follow-up of potential growing skull fractures. Computed tomography (CT) of the head is the primary imaging modality in most circumstances. Some institutions prefer magnetic resonance (MR) imaging, even in emergencies, but this requires controlled sedation or general anesthesia in younger children, and it may not be logistically feasible in an emergency setting. There are clear benefits of MR imaging, though, particularly for nontraumatic hematomas, the underlying cause of which can be more thoroughly investigated. The characteristics of blood products on MR imaging depend on the MR imaging sequence and time after bleed. In many ways, head CT is simpler and quicker, and it remains the standard for emergency evaluation. However, concerns about the radiation dose delivered to the developing brain are growing.^{1,2}

The most important imaging characteristics to assess are the following: hematoma size, regional location (left or right, posterior fossa or supratentorial); layered location (epidural, subdural, parenchymal, subarachnoid/intraventricular); local mass effect and distortion of the brain; comorbid brain swelling or hydrocephalus; and any additional pathology associated with the cause of the hematoma. The size of the hematoma can be estimated by the ABC/2 rule: *A* measures the longest diameter of the hematoma, *B* measures the diameter perpendicular to the *A* line, and *C* measures the number of slices over which the hematoma is visible multiplied by the slice thickness in centimeters. If the image slice contains 75% or more of the hematoma volume at its largest, it is counted as 1 full slice; if 25 to 75%, it is counted as 0.5 slice; if less than 25%, it is not counted. The three measurements are then multiplied and divided by 2 to derive a volume in milliliters.³ The rule works best with intraparenchymal hematomas but can be adapted for extra-axial hematomas. Midline shift is measured on axial CT at the third ventricle, septum pellucidum, or pineal gland; it may be greater than the width of the hematoma when hemispheric brain swelling is present. Hematomas are hyperdense on head CT but may be isodense if hyperacute (as on a very early scan), and they lose their density over time. Subdural isodense lesions may be difficult to appreciate before the typical hypodensity of chronic hematomas develops.

55.3 Extracranial Hematomas

Extracranial hematomas seldom require surgery. They typically occur after some form of trauma.

55.3.1 Childhood Posttraumatic Scalp Hematomas

Scalp hematomas are common after childhood trauma and seldom are of any surgical importance other than indicating the severity and location of the trauma. They may overlie a skull fracture. These hematomas may be large because of the vascularity of the scalp and easy accumulation. This is of particular

importance in infants, in whom the blood lost in the hematoma may cause a significant drop in the hemoglobin level. Scalp hematomas sometimes increase in size as they resolve and the clot liquefies. Rarely, they may become secondarily infected. “Raccoon eyes” and the Battle sign (mastoid bruising) may indicate a fracture of the base of the skull.

55.3.2 Neonatal Subgaleal (Subaponeurotic) Hemorrhage

Subgaleal (subaponeurotic) hemorrhage can be life-threatening in neonates because of the wide potential space in which the clot can spread. Unlike the cephalohematoma, it is not limited by suture lines, so that ongoing bleeding may lead to severe anemia and hypotension; therefore, mortality is high. It presents with a diffuse scalp swelling or fluctuant mass, crosses suture lines, and shifts when the child's head is repositioned. It may be associated with a skull fracture or with rupture of an interosseous synchondrosis or emissary veins between the subdural and subgaleal spaces.⁴ Instrumented delivery is a risk factor. Occasionally, surgery may be required to control the bleeding vessels.

55.3.3 Cephalohematoma

Cephalohematomas are localized subperiosteal clots caused by birth trauma, more often associated with instrumented delivery. The hematoma is limited by the adherence of the periosteum at skull sutures and most commonly occurs parietally, sometimes bilaterally. Occasionally, it is significant enough in size to decrease the infant's hemoglobin level, but this is rare; most are asymptomatic and resolve spontaneously over a few weeks. Cephalohematomas sometimes enlarge and/or calcify over time, leaving an unsightly bump in the parietal region. This can be corrected at a later age. Uncommonly, they may become infected, leading to meningitis or osteomyelitis. This rarely requires a diagnostic tap—possibly if there is an increase in size, the development of erythema and/or fluctuance, or delayed resolution or relapse of clinical signs of infection.⁵ Sometimes, there is an associated epidural hematoma at the same site that is in communication with the extracranial lesion. Rarely, a traumatic cephalohematoma may occur in an older child. A cavernous hemangioma of the skull may occasionally look like a cephalohematoma (► Fig. 55.1).

55.4 Intracranial Hematomas

Intracranial hematomas may be traumatic or spontaneous. Many of the principles that apply to the former apply equally to the latter.

55.4.1 Traumatic Hematomas

Basic Surgical Principles

The removal of an intracranial hematoma in trauma usually constitutes an emergency. The patient is transferred to the operating room after resuscitation and head CT. The anesthesiologist must prepare for ongoing resuscitation and potential

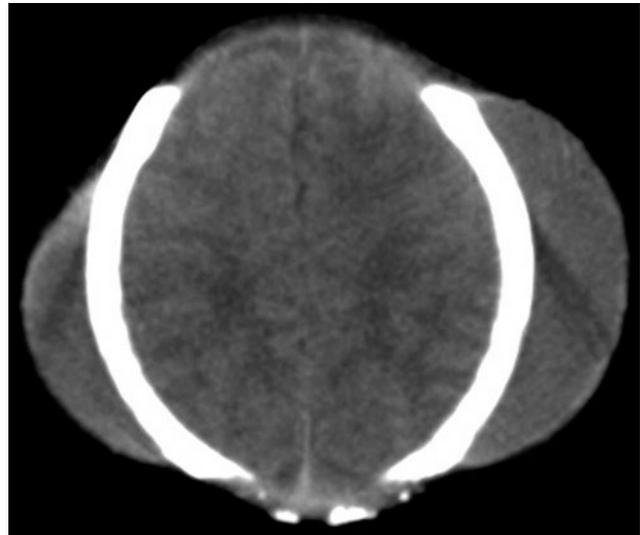


Fig. 55.1 Cephalohematoma. Computed tomographic scan of the head showing the typical appearance of bilateral cephalohematomas.

hemorrhage; large-bore intravenous access and blood cross-match may be needed; clotting must be checked. The head of the operating table is elevated to approximately 20 degrees. Hypertonic saline or mannitol may be used to decrease ICP during preparation for the craniotomy, as may *temporary* mild hyperventilation, while a high inspired fraction of oxygen is maintained. Blood pressure is aggressively maintained, and at no point should the patient be allowed to become even slightly hypotensive. The patient is positioned and the skin flap is planned according to the type of craniotomy planned.

As a general principle, the skin incision and corresponding bone flap should be large enough to allow maximal decompression and the control of bleeding points. For hematomas over the convexity, a large trauma flap (question mark or reverse question mark) incision is performed, for frontal lesions a bifrontal skin incision is made, and for posterior fossa lesions a linear midline or paramedian incision is used. For localized convexity epidural hematomas, a linear incision is sometimes sufficient. For trauma flaps, always ensure that the base of the flap is larger than the length to ensure viability. If the patient's condition is deteriorating rapidly, priority is given to temporal decompression to allow maximal space at the level of the tentorial hiatus before the rest of the craniotomy is completed. Hemostats are used to minimize bleeding from the scalp edges. When turning the scalp flap, take care to not create a sharp fold that reduces blood flow to the flap, especially in very young children. When the bone flap is created, the craniotome is angled to create a bevel that improves contact of the flap when it is replaced. If the dura needs to be opened, ensure that brain swelling has been maximally controlled first (see below). After the hematoma is out, spend time ensuring adequate hemostasis to avoid returning to the operating room to evacuate a re-collection. A subgaleal drain may be used postoperatively (and only for a short period) but should never be a substitute for poor hemostasis. Further details about specific hematomas are discussed in their relevant sections below.

Whether the bone flap is replaced primarily after evacuation of acute subdural or intraparenchymal hematomas depends on

the circumstances. If there is substantial brain swelling or increased ICP (with a monitor in situ), it may be safer to leave the bone flap out so that brain swelling may be controlled in the intensive care unit. In this case, the dura may be enlarged with a pericranial patch. These decisions should be individualized. If the bone is left out, it should be kept in a bone freezer in sterile conditions, or in an abdominal pocket, and replaced as soon as brain swelling has settled (within 4 to 6 weeks if possible). If there are no concerns after the hematoma is evacuated, the bone is replaced.

In general, a lower threshold is used for the evacuation of posterior fossa hematomas for the reasons previously discussed. Mass effect is judged by the effacement and displacement of the fourth ventricle and cisternal spaces and by distortion of the brainstem. This is of particular concern when hydrocephalus is already present. If there is no hydrocephalus and a conservative approach is chosen, repeat the imaging relatively early to detect any increase in the size of the hematoma or the development of hydrocephalus; in these patients, acute coma or apnea may develop. Craniectomy is favored above craniotomy in this location.

Epidural Hematomas

Epidural hematomas (EDHs) are usually secondary to a skull fracture that lacerates a meningeal vessel or venous sinus, or that causes venous blood to accumulate from the fracture edges; however, occasionally there are no associated fractures. In infants, EDHs are less common because the dura is relatively well attached to the skull, and the meningeal vessels are not encased and so are relatively easily displaced rather than torn. An EDH is in many ways the most lethal complication of head trauma that is amenable to surgery, with the potential for complete recovery. An EDH may be associated with very little parenchymal brain injury sustained during trauma but may lead to death due to rapidly developing mass effect. Therefore, the critical determinant is the time to surgery. Classically, a lucid interval may occur; the patient recovers from the initial concussive trauma but then deteriorates as the growing hematoma distorts the brain. Overall mortality is about 5% in children, but this depends on the associated findings and presenting condition.⁶

Although an EDH occasionally may be treated conservatively, the indications for this approach are very specific—the requirements are minimal mass effect of the hematoma (maximum thickness usually < 1 to 1.5 cm), an awake patient, close neurologic observation, and repeated imaging. No formal guidelines exist for children, but the adult literature advises removal of any EDH with a volume of 30 cm³ or more.⁶ When the mass effect of an EDH is evaluated, particular attention must be paid to its location, midline shift, and clinical status of the patient (Glasgow Coma Scale score and focal signs).

The typical appearance on head CT is of a medially convex hyperdense collection. Although EDH commonly occurs frontally or on the convexity, occasionally it occurs in the more dangerous temporal fossa and posterior fossa. The choice of scalp flap is determined by the location and size of the hematoma. A conventional large trauma flap is appropriate for large lesions; however, a focused and quick vertical incision may be used for a patient with a localized clot or for a patient who has deteriorated rapidly and for whom emergent decompression is the

priority. The craniotomy for an EDH should be large enough to evacuate the hematoma and cover the area of probable origin. The surgeon must be particularly careful when fractures cross, or are close to, dural venous sinuses. If so, there must be adequate preparation for potential hemorrhage and a plan to control the sinus. Similarly, depressed fractures must be elevated carefully in cases with significant parenchymal injury, lacerated pial vessels, or proximity to venous sinuses. Hemostasis at the end of surgery must be meticulous. The scalp has been traumatized and tends to be inflamed and prone to oozing. Clotting may be impaired. Bleeding bone edges, especially at fracture sites, should be carefully occluded with bone wax. The use of oxidized cellulose and dural tack sutures at the bone edges of the craniotomy, and perhaps a central hitch suture, may reduce the risk for reaccumulation of the hematoma. If these are used, the surgeon must ensure that placing the suture does not cause a subdural bleed. The bone is replaced and secured with plates and screws (► Fig. 55.2).

Subdural Hematomas

A subdural hematoma (SDH) may be acute (hyperdense on CT), subacute (3 to 14 days, isodense on CT), or chronic (more than 14 days, hypodense on CT). However, although the imaging characteristics may vary during this period, many define an acute SDH up to 14 days after injury.⁷ An SDH is usually located over the convexity of the hemisphere but may occasionally be interhemispheric, on the tentorium, or in the posterior fossa.

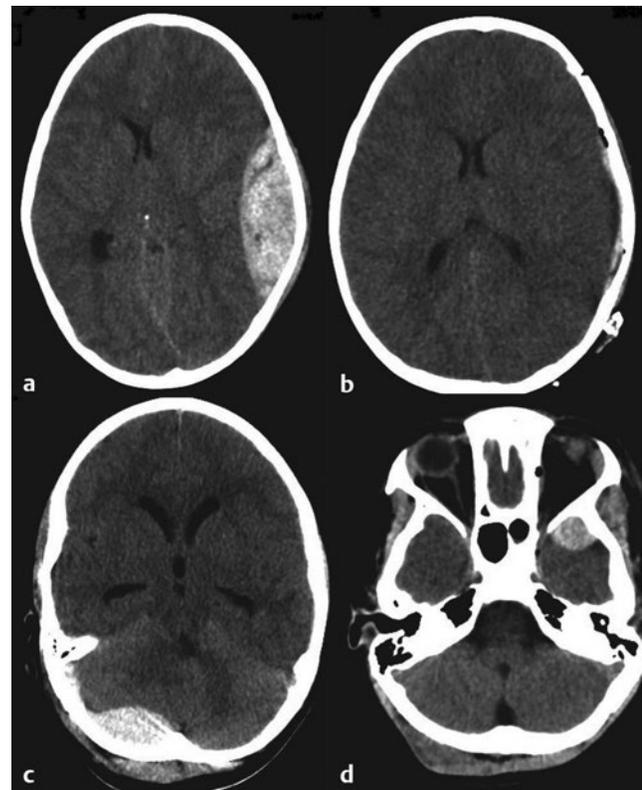


Fig. 55.2 Various epidural hematomas. (a) Left-sided temporoparietal epidural hematoma. (b) Corresponding post-evacuation image. (c) Posterior fossa epidural hematoma. (d) Left temporal tip epidural hematoma.

Acute Subdural Hematomas

Acute SDHs are more likely than EDHs to be associated with underlying brain injury (contusions, brain swelling), so the initial presentation and prognosis tend to be worse; mortality is reported to be as high as 40 to 60%.⁷ The hematoma usually arises from a tear of a cortical bridging vein but may also decompress from a superficially located intraparenchymal lobar hematoma (“burst lobe”). Typically, there is an acceleration/deceleration component to the injury (motor vehicle accidents or falls from a height). Acute SDHs (or acute-on-chronic hematomas, or hematomas of differing ages) in infancy should always raise the suspicion of nonaccidental injury, particularly when there is a discrepancy with the history. SDHs that occur after birth trauma should be considered separately (see below).

The typical appearance of an acute SDH on head CT is that of a crescentic (convex outward), hyperdense clot, often with underlying brain swelling. Over time, the density of the clot decreases; however, a hyperacute clot may also be relatively hypodense. The indications for evacuation of an acute traumatic SDH must be individualized to the patient (age, size and location of the hematoma, level of consciousness and focal signs, associated lesions). However, most clinicians would agree that surgery should be considered for a hematoma with a thickness of more than 5 mm. Official recommendations for adults suggest a thickness of 10 mm or more and/or a midline shift of 5 mm or more.⁷ If the thickness is less than that, surgery is still recommended if there is clinical deterioration.

At surgery, the brain tends to be swollen and hyperemic. The bone flap must be large enough to expose the point of bleeding. If the dura is very tense before opening, it may be prudent to evacuate the clot initially through sequential slits in the dura. Widely opening the dura without control of brain swelling may precipitate the herniation of a congested, hyperemic brain. If the brain is known to be swollen before surgery, the anesthesiologist can take the following measures to assist with the control of ICP: elevating the level of the bed, providing good analgesia and anesthesia, administering hypertonic saline/mannitol at the start of surgery or just before, avoiding hypertension, controlling the CO₂ level, and temporarily hyperventilating the patient when the dura must be opened (at 100% FiO₂). These maneuvers in combination are usually successful in controlling brain swelling, at least for the time period required to open the dura, evacuate the clot, and place an expanded duraplasty. The clot must be evacuated gently under direct vision because sometimes thrombosis has occurred at the point of bleeding but suction of the clot from the vessel may cause rebleeding. This is particularly dangerous when clot beneath the dura, where it is not fully exposed, is suctioned. Caution should be exercised, with gentle suction and wash of the clot. If the brain is swollen, a duraplasty with pericranium or a dural substitute is used to close the dura, and the bone should be left off.

Chronic Subdural Hematomas

Chronic SDHs are most commonly secondary to trauma, ventricular shunts, or surgery. A special consideration is the SDH that occurs after *nonaccidental injury*. The latter condition may present acutely but is commonly seen in a patient with a background of previous injury that has resulted in brain atrophy and bilateral SDH collections with different densities because

the bleeds occurred at different times. The prognosis is often poor as a consequence of multiple episodes of injury, a delayed presentation, and the vulnerability of the young child at presentation. *Anticoagulants* are a risk factor after minor head injury. Subdural collections that develop after overdrainage due to a *ventricular shunt* contain CSF or blood, or a mixture of both. Although these collections sometimes resolve spontaneously, most cause a progressive mass effect or calcify over time. Treatment depends on the size of the collection and the type of shunt used. In general, the drainage of significant collections and upgrade to a higher-pressure valve, programmable valve, or antisiphon device may be indicated.

Chronic SDHs must be distinguished from the benign extracerebral subarachnoid collections of CSF seen in *external hydrocephalus* and the subdural effusions associated with *meningitis*, especially *Haemophilus meningitis*. Nonaccidental injury must also be distinguished from *glutaric aciduria type 1*, a rare metabolic disorder whose radiologic signs may mimic those of the former.⁸

In a chronic SDH, a vascularized membrane develops over the subdural collection as a consequence of the brain's inflammatory response. Repeated bleeds from the vascularized membrane may progressively enlarge the collection. Treatment depends on the underlying condition but may involve a subdural tap through the lateral aspect of an open fontanel, bur hole drainage and irrigation, or placement of a subdural drain or shunt, with correction of the underlying abnormality where appropriate (► Fig. 55.3).

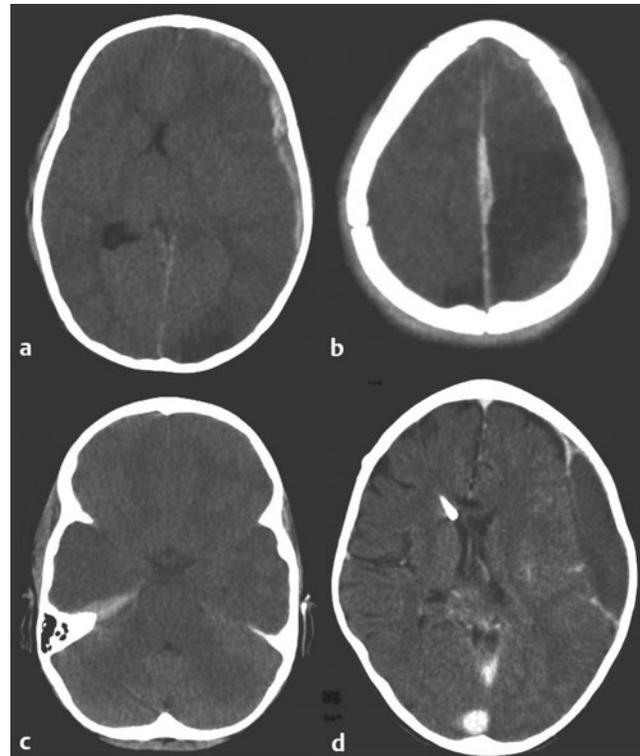


Fig. 55.3 Various subdural hematomas. (a) Swollen brain after trauma, with a left-sided acute subdural hematoma, midline shift, and left occipital hypodensity. (b) Interhemispheric subdural hematoma and bilateral hypodensities. (c) Subdural hematoma on the right tentorium. (d) Chronic subdural hematoma after cerebrospinal fluid overdrainage related to ventriculoperitoneal shunting.

Intracerebral Contusions and Hematomas

There is no clear distinction between contusions and intracerebral hematomas (ICHs) in trauma. Contusions tend to be smaller and mixed with disrupted brain tissue, whereas hematomas are larger, coalesced, more homogeneous collections of blood clot with discrete margins. Intracerebral lesions may be associated with penetrating or blunt trauma. Penetrating trauma is uncommon in children but easily missed. Often, the scalp wound is small, and penetration of the brain is easy because of the thin scalp and skull. The point of skull penetration may be very focal and not easily appreciated on clinical examination (especially if behind the hairline) or plain radiographs. Deep penetration of the brain with a sizeable contusion or track hematoma may be associated with a very small skull defect. Gunshot wounds and assault stabs are obvious mechanisms, but unusual objects may be the cause (e.g., tent peg, nail, pen). Blunt trauma causes focal or diffuse injury. Focal injury is concentrated at the site of impact, at times associated with a contrecoup lesion. Diffuse injury contusions typically occur in the orbitofrontal and temporal regions or in relation to the base of the skull, gray–white interface, corpus callosum, or brainstem. Occasionally, large contusions occur deep in the basal ganglia. Where there are substantial contusions in the brain, the threshold for repeated imaging should be low because “blossoming” of the contusions with increased mass effect may be seen. Sometimes, the radiographic appearance of contused brain may develop only after the initial imaging. The pericontusional area may be similar to an ischemic stroke penumbra, in which tissue is viable but threatened by secondary biochemical and inflammatory changes, so that it is progressively incorporated into the damaged area. In this situation, there is a risk for both low and high blood pressure, both of which may cause progressive enlargement of the contusion by ischemia and vasogenic edema, respectively.⁹

Indications for surgery are more difficult than those for extra-axial hematomas; adult guidelines suggest surgery for (1) frontal and temporal lesions larger than 20 cm³ with midline shift of 5 mm or greater and/or cisternal compression and (2) any lesion of 50 cm³ or more. In reality, factors influencing the decision for surgery should include altered level of consciousness, a deteriorating condition, focal signs, coalescence of the hematoma, location and accessibility of the hematoma, and perhaps increased ICP in patients who are being monitored.¹⁰ The surgical principles are similar to those for an acute SDH. In addition, the corticectomy is chosen to achieve the shortest distance to the lesion and protect eloquent brain. Expansive duraplasty and removal of the bone may be considered for the swollen brain (► Fig. 55.4 and ► Fig. 55.5).

Subarachnoid Hemorrhage

Traumatic subarachnoid hemorrhage (SAH) is rarely clinically significant. It occurs most commonly in diffuse injury,

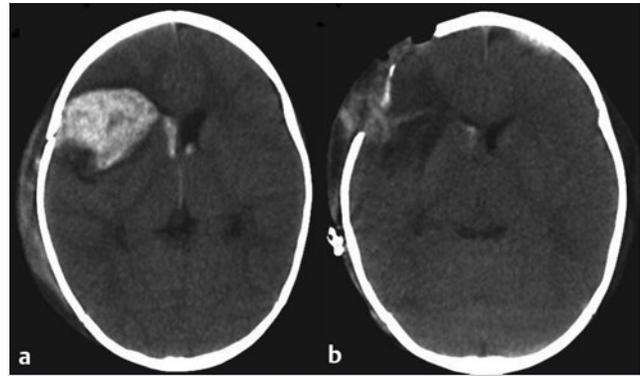


Fig. 55.4 Discrete posttraumatic intracerebral contusion/hematoma. (a) Traumatic intracerebral hematoma in an injury caused by a falling pole. (b) The hematoma has been evacuated.

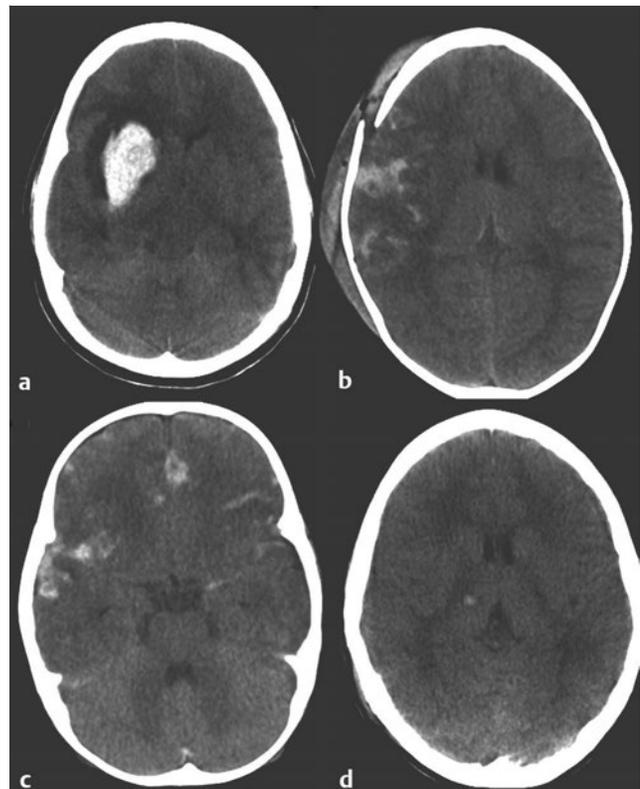


Fig. 55.5 Variations of traumatic contusions. (a) Deep, discrete intracerebral hematoma (motor vehicle accident). (b) Regional, indistinct contusion. (c) Multiple small contusions in the frontal and temporal lobes. (d) Small single punctate contusion in the right thalamus.

usually manifesting as a small amount of blood in the interpeduncular space or in the ambient and quadrigeminal plate cisterns. Some suggest that traumatic vasospasm is relatively common after childhood trauma on investigation¹¹;

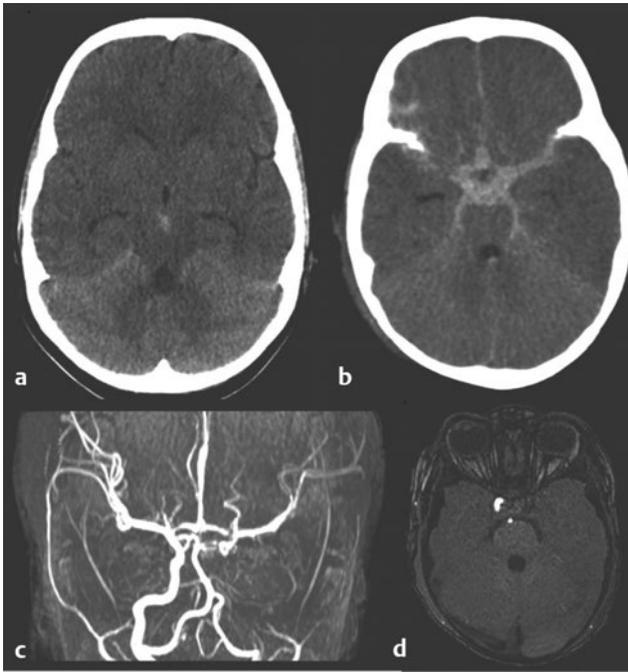


Fig. 55.6 Traumatic subarachnoid hemorrhage. (a) Small amount of subarachnoid blood in the interpeduncular fossa (traumatic). (b) A more substantial traumatic subarachnoid hemorrhage. (c,d) Computed tomographic angiograms of the patient in (b), demonstrating absence of the left carotid.

however, others suggest that this is rare.¹² Unlike in adults, clinical vasospasm appears to be uncommon in children, regardless of the cause. Traumatic SAH rarely causes hydrocephalus in children. If there is substantial SAH (► Fig. 55.6B), the patient should be investigated for blunt cerebrovascular injury with MR or CT angiography.¹³ The management of SAH with nontraumatic causes is discussed below (► Fig. 55.6).

Intraventricular Hematomas

Intraventricular hemorrhage (IVH) may occur after trauma, prematurity (germinal matrix hemorrhage), surgery (ventriculoperitoneal shunt, external ventricular drain, tumor surgery), vascular malformations, and aneurysms. In trauma, IVH is associated with diffuse injury and rarely requires intervention. IVH rarely causes hydrocephalus in trauma but does so commonly when it is associated with other conditions. Management depends on the etiology but in general requires hydrocephalus-related increased ICP. External ventricular drainage reduces ICP and helps clear blood in the ventricles; however, catheters are prone to blockage by blood clot. Other techniques have been tried, including endoscopic washout of the clot and the intraventricular administration of thrombolytics, such as tissue plasminogen activator (tPA). Unfortunately, these do not appear to offer a clear enough advantage to warrant widespread adoption.

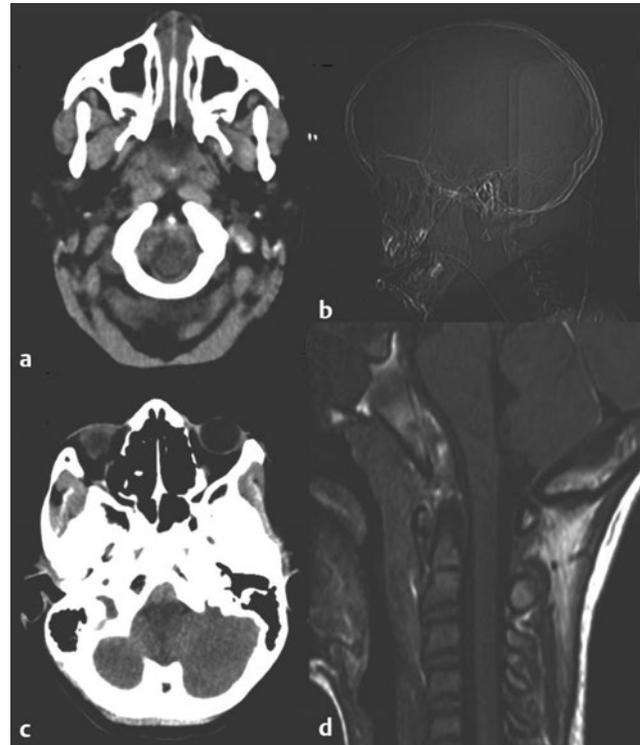


Fig. 55.7 Retroclival hematomas. (a) Axial computed tomographic (CT) scan of the head showing a collection of blood ventral to the lower brainstem. (b) Atlantoaxial disruption in the same patient. (c) CT scan of the head of a different patient showing a more subtle image of blood ventral to the brainstem. (d) Magnetic resonance image of the same patient showing the retroclival hematoma ventral to the brainstem.

Retroclival Hematomas

Retroclival hematomas are unusual trauma-related bleeds, more common in children than adults.¹⁴ The mechanism is unclear but likely related to the anatomical characteristics of the pediatric craniocervical junction, possibly disruption of the tectorial membrane and bleeding from the basilar venous plexus. The hematoma itself rarely requires evacuation, but it is an important diagnosis to make because there may be underlying atlanto-occipital or atlantoaxial disruption (► Fig. 55.7B). Often, the bleed is apparent only on the very lowest axial slices of conventional trauma head CT scans (► Fig. 55.7C), so it should be routine practice to look for these hematomas. When a retroclival hematoma is suspected, MR imaging must be obtained (► Fig. 55.7).

55.4.2 Spontaneous Hematomas

Hemorrhage accounts for nearly half of all pediatric strokes, with mortality as high as 25% and residual disability in 40% of survivors.¹⁵ Management depends not only on the characteristics but also, more importantly, on the etiology of the hematoma (see box “Etiology of Spontaneous Cerebral Hemorrhage in Children (p. 724)”).

Etiology of Spontaneous Cerebral Hemorrhage in Children

- Postoperative
- Vascular malformations
 - Arteriovenous malformations
 - Arteriovenous fistulas
 - Developmental venous anomalies
 - Capillary telangiectasia
 - Cavernoma
- Intracranial aneurysms
 - Saccular
 - Dissecting
 - Infective
 - Posttraumatic
- Brain tumors
- Hematologic
 - Sickle cell disease
 - Thrombocytopenia
 - Hemolytic uremic syndrome
- Coagulation abnormalities
 - Hemophilia
 - Protein C and protein S deficiency
 - Vitamin K deficiency
 - Disseminated intravascular coagulation
 - Hepatic failure
 - Iatrogenic
- Hemorrhagic transformation of an infarct
- Sinovenous thrombosis
- Hypertension
- Neonatal hemorrhage
 - Prematurity-related germinal matrix intraventricular hemorrhage
 - Clotting abnormalities
 - Hemophilia
 - Thrombocytopenia
 - Hemorrhagic disease of the newborn
 - Birth trauma
- Vasculopathy
 - Moyamoya disease
 - Inflammatory vasculitis
 - Herpes simplex encephalitis
 - Other infections
 - Systemic lupus erythematosus
- Other systemic disorders
 - Extracorporeal membrane oxygenation (ECMO)
 - Cancer
 - Substance abuse
 - Congenital cardiac disease
- Idiopathic

In a series of 68 children with spontaneous intracranial hemorrhage, congenital vascular anomalies were present in 42%, hematologic or coagulation disorders in 32%, and an underlying tumor in 13%. Unlike in adults, hypertension is uncommon as a cause of intracranial hemorrhage in children. Management largely depends on the etiology of the bleed, which may or may not be clear. Basic principles are resuscitation, control of ICP,

etiologic diagnosis, and definitive management of the underlying condition.

Definitive diagnosis starts with a good *history*, including any previous intracranial conditions diagnosed, drug history (especially anticoagulants and drug abuse), systemic or genetic conditions known to be associated with intracranial lesions or coagulation abnormalities, underlying illness (cardiac lesions, chronic pulmonary disease, connective tissue disorders), family history, and history of previous trauma. The *examination* includes a full neurologic examination, examination of the heart and chest, and examination for signs of systemic conditions. The complete blood cell count and coagulation parameters must be checked.

Imaging is central to the diagnosis of the underlying condition and surgical evaluation of the hematoma. It is directed by the likely etiology but may include initial head CT for emergent management, CT angiography, MR imaging, MR angiography, MR venography, and digital subtraction angiography. In general, the principles of management are similar to those for trauma but are subject to consideration, investigation, and sometimes primary treatment of the underlying condition.

55.4.3 Specific Conditions Causing Spontaneous Hemorrhage in Children

Prematurity-related ICH and IVH are common in pediatrics, arising from bleeds in the germinal matrix of the brain. A fuller discussion of these is located elsewhere in this book.

Pediatric *aneurysms* are rare, accounting for 5 to 7% of all aneurysms reported. The distribution of ages at presentation is biphasic—aneurysms occur most often before age 2 or after age 10. Children are more likely than adults to present with either IVH or ICH rather than SAH, and also with giant aneurysms or posterior circulation aneurysms. Associated conditions include coarctation of the aorta, fibromuscular dysplasia, autosomal-dominant kidney disease, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum. The pathology of the aneurysm may be dissecting, saccular, infectious, or posttraumatic. Traumatic aneurysms may occur with penetrating injury and fractures of the base of the skull, and dissection may be due to blunt trauma. *Infectious aneurysms*, *infective aneurysms*, and *mycotic aneurysms* are all terms for the immune complex-related false aneurysms that result from an adventitial disruption, mostly due to infectious endocarditis but also to chronic pulmonary disease and intravenous drug abuse. The risk for endocarditis, and so for intracranial infectious aneurysms, is related to the underlying frequency of rheumatic heart disease and congenital heart lesions in the population. Infectious aneurysms may occur at almost any time during the course of the disease—before, during, and after antibiotic treatment for the cardiac valvular lesions. Vertobasilar dissections occur more commonly in boys and present with hemorrhage in about one-third of cases; the others present with headache and vertigo or mass effect.¹⁶

Most aneurysms in children are treated endovascularly. Surgical management of the hematoma depends on its location and size, as well as the primary treatment of the aneurysm. When possible, the aneurysm should be controlled before clot evacuation, should the latter be necessary. If there is no time for

an endovascular procedure (or no expertise immediately available) in a patient whose condition is deteriorating with mass effect, a conservative operation to reduce ICP may be prudent, without an attempt to remove all of the hematoma and risk rebleeding from the aneurysm (► Fig. 55.8 and ► Fig. 55.9).

Vascular malformations also are rare. However, it is estimated that 20 to 40% of all *arteriovenous malformations* (AVMs) or *arteriovenous fistulas* (AVFs) are diagnosed in childhood.^{17,18} Most present with hemorrhage (three-quarters), the rest with seizures or mass effect. Hereditary hemorrhagic telangiectasia should be considered in patients with multiple central nervous system AVMs. Familial AVMs have also been described, unre-

lated to known specific genetic conditions. In children with known AVMs, the annual hemorrhage risk is 2 to 4%, and hemorrhage is reported to be fatal in as many as 25%.¹⁷ *Cerebral proliferative angiopathy* is a relatively new term used to describe vascular malformations that present in predominantly young patients; they are associated with diffuse angiogenesis, small-caliber of feeding vessels and draining veins, and chronic cortical ischemia.¹⁹ A vein of Galen malformation is a choroidal type of AVM involving the forerunner of the vein of Galen, as distinguished from an AVM with venous drainage into a dilated but already formed vein of Galen. Vein of Galen malformations account for about half of all AVMs in children.¹⁸ Many vascular malformations are associated with a dilated vein of Galen but are not classic vein of Galen malformations. They present rarely with hemorrhage, and more commonly with cardiac failure, hydrocephalus, or cerebral venous hypertension. Arteriovenous fistulas are rare, superficial, and fed by pial cortical vessels; about one-quarter are associated with hereditary hemorrhagic telangiectasia.¹⁸ Arteriovenous fistulas may present with a bleed, venous hypertension, cardiac insufficiency, macrocrania, epilepsy, mass effect, or a “sound in the head.” The management of AVMs and AVFs is usually endovascular. Developmental anomalies are extreme variations of normal transmedullary venous drainage that are usually benign but may become symptomatic, presenting with either hemorrhage or venous congestion/infarction²⁰ (► Fig. 55.10).

Cavernomas, or *cavernous malformations*, are estimated to have a prevalence of about 0.4 to 0.8%, which increases with age. Symptomatic cavernomas usually present with either hemorrhage or epilepsy; lesion size and location are the important factors associated with symptoms. The hemorrhage rate in children and young adults varies from 0.2% per patient-year in those with incidentally discovered cavernomas to 8% per patient-year in those with symptomatic cavernomas.²¹ The rate per patient-year is higher than the rate per cavernoma-year, reflecting the higher risk for patients with multiple cavernomas. Multiple cavernomas may occur in familial cases and with certain sporadic genetic mutations. Radiotherapy in early life increases the risk for the development of a cavernoma in later life.²² Cavernomas are notable in survivors of medulloblastomas; however, most of them tend to follow a benign course.²³ The lesions often increase in size over time because of repeated episodes of bleeding and calcification. Head CT and MR imaging show well-demarcated lesions that have a typical “popcorn” appearance, with calcification and evidence of repeated microhemorrhages; the core has a heterogeneous appearance and is

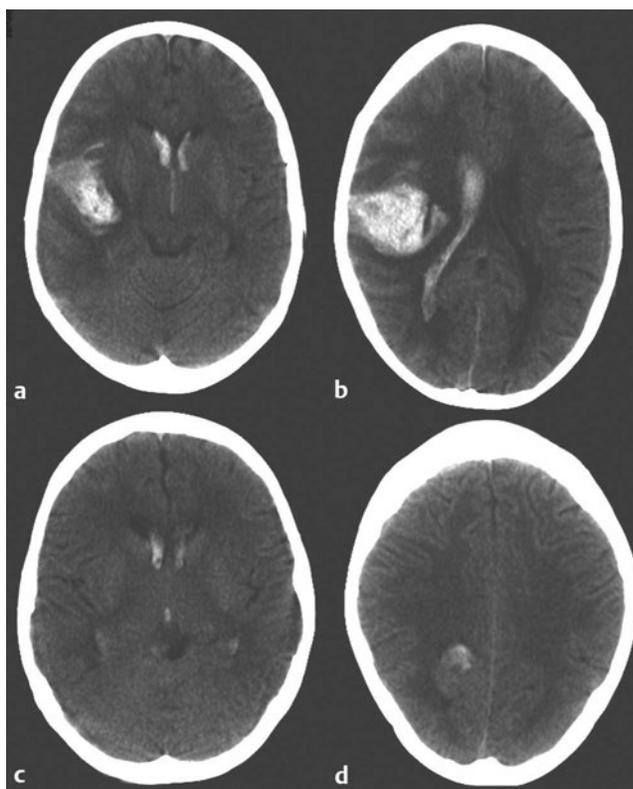


Fig. 55.8 Aneurysmal bleeds in two children. (a,b) Intracerebral hematoma and intraventricular hemorrhage in a patient with an infectious aneurysm, several weeks after the start of antibiotic therapy for infective endocarditis. (c,d) Bleeds due to dissecting aneurysms.

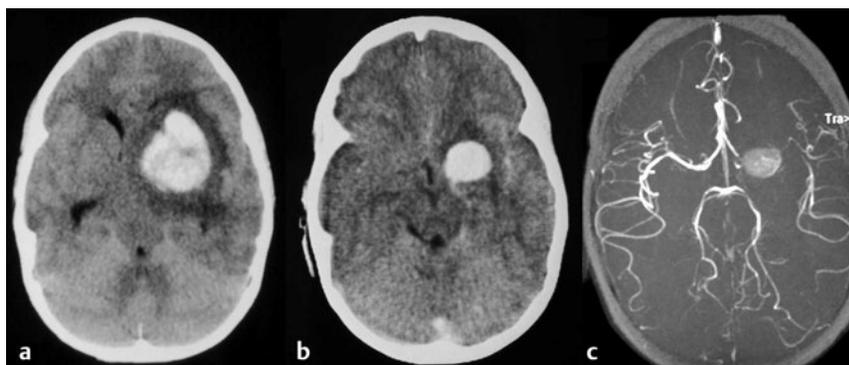


Fig. 55.9 Saccular aneurysm in an 8-year-old boy. (a) Computed tomographic CT scan of the head showing a spontaneous deep hematoma. (b) Contrast-enhanced CT scan of the head showing a giant aneurysm after resolution of the hematoma. (c) Magnetic resonance angiogram showing the same aneurysm.

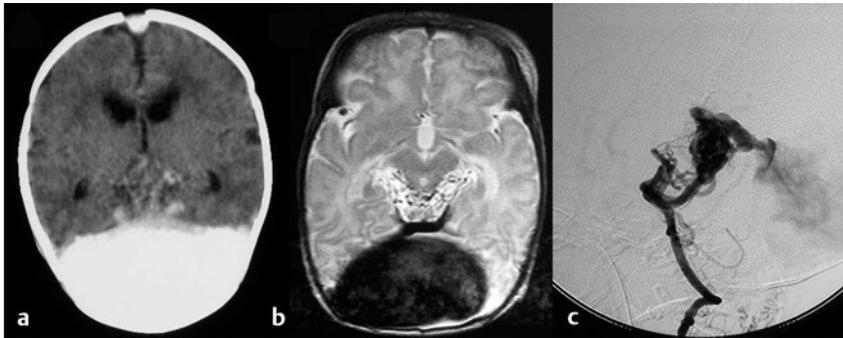


Fig. 55.10 Dural fistula in an infant. The scans show a complex dural fistula in the region of the vein of Galen and torcular in a 3-week-old child with multiple internal and external carotid arterial feeders. (a) Computed tomographic scan of the torcular massively expanded with blood. (b) Similar magnetic resonance image also demonstrates one of the fistulous connections. (c) Angiographic findings of a right vertebral run and one of the fistulas.

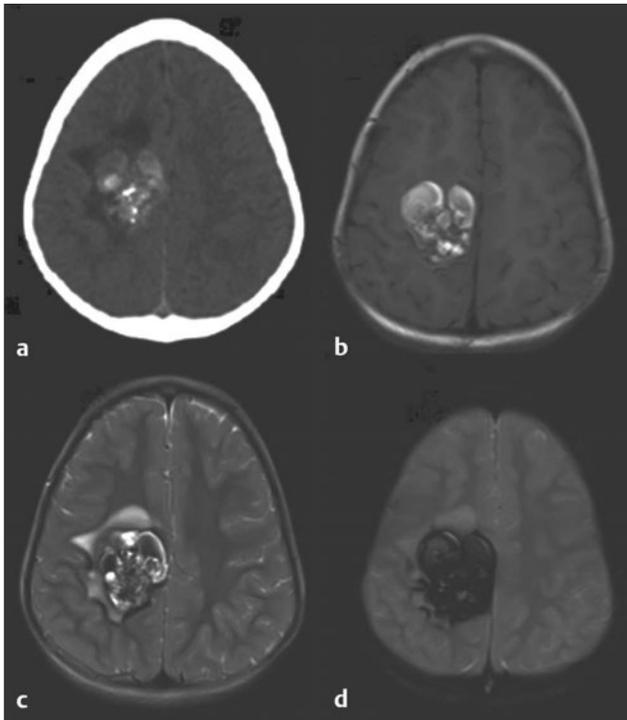


Fig. 55.11 Cavernoma in a 4-year-old girl. (a) Computed tomographic scan of the head showing a mixed-density lesion with some blood and calcification. (b) Axial magnetic resonance (MR) image showing a T1 bright lesion with surrounding hematoma and the typical “popcorn-like” character. (c) Axial T2 MR image of the same lesion. (d) Gradient-echo MR imaging sequence demonstrating the blood product.

surrounded by a hemosiderin rim. The gradient-echo appearance is classic. The decision to remove a cavernoma surgically must take into consideration the expected natural history and the likely morbidity of surgery, which is primarily determined by the location of the lesion (► Fig. 55.11).

Tumor-related bleeds depend on the location and nature of the tumor. In general, bleeds are a rare presentation of pediatric intracranial tumors, tending to occur with more aggressive, vascular tumors. Management depends on the clinical presentation, histology of the tumor, mass effect, and location of the clot. Early management targets relief of raised ICP or local mass effect. It may not be ideal to remove the tumor in the same session, so a relatively conservative approach may be indicated to decompress the hematoma emergently. However, it must be

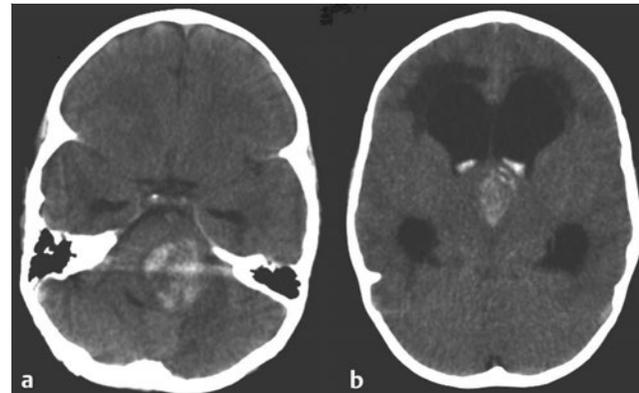


Fig. 55.12 Hematomas within tumors. (a) Computed tomographic (CT) scan of a 3-year-old boy with a spontaneous bleed in a posterior fossa ependymoma. (b) CT of the head of a 5-year old girl showing a bleed within a hypothalamic astrocytoma, with resultant intraventricular hemorrhage and hydrocephalus.

remembered that the risk for bleeding into the surgical cavity is higher with residual tumor (especially if malignant). Intraoperative hemostasis is critical, and pain-related hypertension in the postoperative period must be avoided because it increases the risk for a postoperative bleed. Occasionally, embolization before resection may be suitable for highly vascular tumors, such as choroid plexus tumors, to minimize intraoperative bleeding, especially in very young patients (► Fig. 55.12).

Hematologic Abnormalities

Idiopathic thrombocytopenic purpura is an autoimmune disorder, usually associated with a preceding viral infection. It is one of the most common acquired bleeding abnormalities in children. Intracranial hemorrhage is an uncommon complication but carries a high mortality rate. Surgical management is considered only when absolutely necessary and requires coverage with platelet transfusions. Thrombocytopenia secondary to hematologic malignancies (► Fig. 55.13) presents similar management dilemmas. *Neonatal thrombocytopenia* is discussed below. *Hemophilia A* (clotting factor VIII) and *hemophilia B* (clotting factor IX) are genetic disorders with a relatively high risk for intracranial hemorrhage, especially in neonates, but also following minor head injury in older children.²⁴ Treatment again depends on temporary reversal of the coagulopathy. *Vitamin K deficiency* is discussed below.

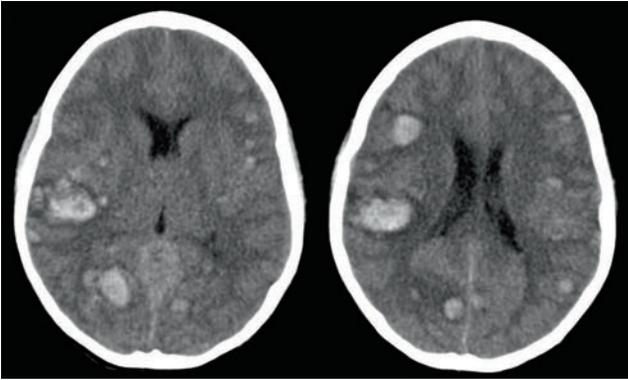


Fig. 55.13 Thrombocytopenia due to acute myeloid leukemia resulting in multiple intracranial bleeds in a child with an acute deterioration in consciousness.

Sinovenous Thrombosis

Thrombosis of the venous sinuses and deep and superficial veins may be associated with several disorders and conditions—dehydration, hypoxia, anemia, malignancies, cardiac disease, renal disease, head and neck infections, systemic diseases (e.g., systemic lupus erythematosus), inflammatory bowel disease, metabolic conditions—and with drugs (e.g., steroids).¹⁷ The presentation depends on the venous structure involved and may include any variety of ICH, SAH, SDH, brain swelling, hydrocephalus, and infarction. Typical imaging shows linear densities in deep and superficial veins on uncontrasted head CT, an empty delta sign as a filling defect in the posterior part of the superior sagittal sinus on contrasted CT (but which can be falsely positive), and absence of flow in the sinus on MR or CT venography.

Extracorporeal membrane oxygenation is used to support infants with refractory respiratory failure, but substantial changes in the cerebral blood flow may lead to intracranial complications, including cerebral hemorrhage, ischemia, and hemorrhagic transformation of an ischemic area.²⁵ Intracranial bleeds in patients with extracerebral *cancer* may result from the effects of chemotherapy, sepsis, and metastasis. *Drug abuse* is a major risk factor for ischemic strokes and cerebral hemorrhage in adolescents, usually due to the pharmacodynamic effects.²⁶ The drugs include cocaine, methylphenidate, and phencyclidine. Intravenous drug abuse also carries a risk for endocarditis and infectious aneurysms.²⁷ Prescription drugs also carry a risk, such as phenylpropanolamine²⁸ and, of course, anticoagulant therapy.²⁹

Neonatal Hemorrhage

Neonatal hemorrhage deserves special consideration because of the different pathologies and presentations. The true incidence of neonatal hemorrhage is not known because many episodes are asymptomatic. For subdural hemorrhage, the incidence may be as high as 8% in otherwise normal terms infants.³⁰ In fact, in one prospective study of vaginally delivered asymptomatic normal infants who underwent MR imaging, 26% had some form of intracranial hemorrhage.³¹ Symptomatic hemorrhage is much less common; an average incidence of about 3.8 per 10,000 live births is reported.³⁰

Traumatic hemorrhage is usually the consequence of birth trauma. Risk factors include instrumented delivery, macrosomia, prematurity, abnormal fetal presentation, and prolonged labor.⁴ Birth trauma may occur in as many as 2 to 7% of all deliveries and is associated with increased mortality and morbidity.³² The pathology spectrum ranges from caput succedaneum and cephalohematoma to subgaleal hemorrhage and subarachnoid, subdural, and intraparenchymal hemorrhage, with or without skull fracture.

Hemorrhage in term infants has a particular predilection for the posterior fossa, often the region of the falcotentorial junction. Deformation of the skull as it passes through the birth canal, especially vertical molding, causes dural tension, with tearing of veins and dural sinuses. In occipital osteodiasis, one particular mechanism, the squamous and lateral parts of the occipital bone separate, leading to rupture of the occipital sinus and direct trauma to the cerebellum.⁴

The pattern of SDHs in infants is different from that seen in older children, and they are more common than previously thought. They are the most common form of intracranial hematoma in term infants and are usually associated with instrumented delivery or cesarian section after failed labor (which may represent an increased risk for difficult labor regardless of the eventual method of delivery). Occasionally, they may be diagnosed in utero or without excessive birth trauma in asymptomatic infants. EDH in neonates is uncommon because the meningeal vessels are not incorporated into the bone and tend to be displaced away from the skull.

Unlike term infants, 80% of preterm infants with IVH have associated *germinal matrix hemorrhagic* infarction; this is primarily a disorder of preterm (50%) compared with term infants (4%).³⁰ *Thalamic or intraventricular hemorrhage* in term newborns is less common. It may arise from several sites—the choroid plexus, thalamus, and subependymal germinal matrix (associated with birth trauma and birth asphyxia)—but in 25% of cases the cause is unknown (it may be cryptic hemangioma of the choroid plexus). Overall, IVH in term infants is reasonably common, but the vast majority of cases are asymptomatic. *Vitamin K deficiency* (hemorrhagic disease of the newborn) may result from an inadequate supply in breast milk, decreased production by intestinal bacteria (antibiotics), malabsorption syndromes or chronic diarrhea, and iatrogenic causes.

Bleeding disorders in neonates may present with intracranial hemorrhage. The most common causes include hemophilia, thrombocytopenia, and hemorrhagic disease of the newborn. Neonatal hemophilia commonly presents with iatrogenic or intracranial hemorrhage, whereas in older children and adults, hemarthrosis is more common. Thrombocytopenia is common in preterm neonates, in whom it may be early (having antenatal causes and usually resolving without treatment) or late (after 72 hours, usually associated with bacterial infection, necrotizing enterocolitis, or congenital infection), and tends to be more severe.³³ It is much less common in term neonates, in whom autoimmune thrombocytopenia is the most important cause.

The *clinical features* of hemorrhage in neonates are different from those in older children. Neonates tend to present with more subtle or nonspecific signs, including irritability and failure to suck. They may also present dramatically, with cardiovascular

collapse, respiratory distress or apnea (especially when the hemorrhage is associated with heart rate irregularities), seizures, and a bulging fontanel. Cranial ultrasound is the first-line investigation in neonates because of the open fontanel, portability, low costs, and absence of radiation. Treatment is directed by the size and location of the hematoma, clinical status, and underlying etiology. The risk for a poor outcome in neonates with symptomatic hemorrhage is high, given their young age and vulnerable brain.

Pearls

- Extracranial hematomas are rarely a surgical problem; however, neonates can bleed acutely into the subgaleal space.
- Control of raised ICP is the first priority in managing intracranial hematomas.
- Time is critical—delay in evacuating an intracranial hematoma may lead rapidly to brain herniation, brain ischemia, and death.
- The principles of management in trauma are resuscitation (especially avoidance of hypoxia or hypotension), early imaging, and surgical evacuation of the hematoma.
- The principles of trauma surgery are a large skin and bone flap, control of bleeders, intraoperative control of brain swelling (anesthesiology), and dural enlargement if there is brain swelling with or without the bone flap left off.
- Vascular anomalies, hematologic disorders, and underlying tumors account for most spontaneous hematomas in children.
- The key to managing spontaneous intracerebral hemorrhage is diagnosis of the underlying condition. The likely diagnosis is suspected from the history and basic imaging, which then determines subsequent management.
- Very large hematomas may present with surprisingly nonspecific signs in young children.

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56 Traumatic Brain Injury in Children: Critical Care Management

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56.1 Epidemiology

Traumatic brain injury (TBI) remains the leading cause of death between the ages of 1 and 18 years. In the United States, one TBI has been reported to occur as frequently as every 15 seconds, with one death resulting every 12 minutes. According to the Centers for Disease Control, each year in the United States approximately 1 million infants, children, and young adults sustain a TBI. Of these, 600,000 will come to medical attention and 250,000 will be admitted to the hospital; 30,000 will be permanently disabled and 7,000 will die. Severe TBI in children is responsible for nearly \$20 billion annually in health care costs. International efforts to define the mortality and morbidity burden of severe TBI have proved fruitful. Aggressive prevention efforts and new insights into the pathophysiology of primary injury (moment of impact), as well as the evolution and reduction of secondary injury, continue to show great promise. However, only in the past 15 years has direct scientific inquiry begun to address the question of the optimal treatment of severe TBI in children.

56.2 Development of International Standards: Evidence-Based Management Guidelines and Common Data Elements

In 1996, Bullock and colleagues,¹ using the principles of contemporary evidence-based medicine, published the first guidelines for the management of adult severe TBI. Before this seminal effort, which included the input of international experts, the management of severe TBI in adults was found to be highly heterogeneous, colloquial, and not evidence-based. The panel reviewed studies relevant to the management of head-injured patients and stratified the data based on the quality of evidence. The stratification of existing head injury–related publications according to quality yielded a summary of practical, weighted consensus treatment guidelines and assisted in the charting of directions for future research and funding efforts. Although international acceptance and application were initially variable, independent evaluations of the impact of the application of these guidelines have consistently demonstrated significant reductions in mortality, adjusted length of stay, and costs.^{2,3}

In 2000 and again in 2012, similarly configured panels of pediatric experts were convened to develop consensus guidelines for the treatment of severe TBI in infants, children, and young adults.^{4–23} The developing brain has unique anatomical and cerebrovascular characteristics that warranted the development of independent guidelines. Additionally, the response to trauma of pediatric patients—particularly infants and young children—mandates that they not be treated as “little adults.” The

evidence-based approach was reapplied to the relevant literature on pediatric brain trauma, and “Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents” was published. Three degrees of evidence quality were applied throughout the process (see box “Evidenced-Based Medicine Levels of Evidence in Severe Traumatic Brain Injury (p. 729)”), and three classes of evidence were identified (see box “Classification of Evidence in Severe Traumatic Brain Injury (p. 729)”). In the most recent edition, the pediatric guidelines encompass 15 topics deemed to be imperative to improving outcome. These topics form the scaffolding for this chapter.

Evidenced-Based Medicine Levels of Evidence in Severe Traumatic Brain Injury

- Level 1
 - Sufficient evidence exists that these therapies “should be done.”
- Level 2
 - Sufficient evidence exists that these therapies “should be considered.”
- Level 3
 - Sufficient evidence exists that these therapies “may be considered.”

Classification of Evidence in Severe Traumatic Brain Injury

- Randomized controlled trials completed; may still lack sufficient numbers and have methodologic inadequacies
- Clinical studies based on clearly reliable data; prospective collection with retrospective analysis acceptable
- Retrospective analyses; case series/reports, databases, registries, expert opinion

During the past several decades, it has been recognized that the analysis of clinical studies in TBI has been hampered by a lack of clarity in the definitions of patient characteristics and by inconsistencies in reporting important factors between studies. Specifically, despite the best intentions of authors to fully describe (1) the population under study, (2) the clinical variables collected, and (3) the outcomes that were observed, comparisons of the results of clinical studies suffered from ad hoc editorial decisions made during manuscript preparation. In seminal work on this topic, Lingsma and colleagues took several years to painstakingly combine data from 10 randomized controlled trials (RCTs) and three observational trials in the International Mission on Prognosis and Clinical Trial in Traumatic Brain Injury (IMPACT) study.²⁴ This yielded an analysis of 9,578 patients enrolled at 265 clinical sites that found striking differences in unfavorable outcome rates between centers in the United States and Europe. This led Maas and colleagues to develop common

definitions of various aspects of TBI care, the so-called common data elements (CDEs), to improve the uniformity of defining TBI care and data collection.²⁵ In pediatric TBI, CDEs for acute data collection, imaging, biomarkers, and outcomes were recently published in liaison with the National Institute of Neurological Disorders and Stroke (NINDS), and these elements will be required for future funded clinical trials.^{26–29}

The goals of contemporary pediatric neurocritical care are the early identification and management of surgically evacuable lesions and the prevention of secondary injury. Pediatric neurocritical care strategies for severe TBI have evolved from strategies for exclusively supportive care to those attempting to (1) optimally match substrate delivery and cerebral metabolism with the use of multimodal monitoring, (2) prevent herniation by anticipatory clinical strategies and meticulous nursing care, and (3) target specific mechanisms involved in the evolution of secondary injury with novel or experimental therapy. The re-evaluation of current approaches, the role of newer technologies, and the differences between adults and children will be highlighted.

56.3 Clinical Presentation

The rapid identification of injuries and the assessment of their severity are essential to minimize the risk for undertreating evolving clinical conditions and to ultimately optimize outcomes. The Glasgow Coma Scale (GCS) score³⁰ (► Table 56.1), first described in 1974, remains a critical tool for communicating the severity of neurologic injury after TBI. Hypoxemia, shock, and hypotension all reduce the GCS score. Optimal resuscitation, therefore, is an important prerequisite to assigning the best GCS score. In preverbal children, the GCS score has been modified to allow a score of 5 for the cooing child. The modified GCS score for infants and children (► Table 56.1), although convenient, has not been subjected to extensive peer review.^{31,32} For this reason, the infant GCS score is best applied by those familiar with the management of young children. The best motor score is the most predictive component of the GCS.³³ Additionally, the AVPU (awake, [responds to] verbal, [responds to] pain, unresponsive) scale provides a rapid, albeit crude, assessment of neurologic status. Moreover, the pupillary examination is an

essential aspect of the physical examination to triage children with TBI.³⁴ In a rigorous study of 500 normal subjects, Meyer et al demonstrated that anisocoria of less than 1 mm is clinically unimportant. Sparse evidence exists regarding the prognostic significance of the light reflex. Of note, hypotension, hypothermia, and hypoxemia all confound the pupillary light reflex.³⁵ Optimal resuscitation, therefore, remains the clinical linchpin on which all other assessments, diagnoses, and prognoses rest.

The accurate assessment of the child with TBI is essential to developing a comprehensive care plan that includes the necessary imaging, invasive procedures, and medical and surgical therapies. To date, this has largely been based on the physical findings and the GCS score, as outlined above. In particular, the GCS score combined with signs of acute brain dysfunction aid in the assessment of patient acuity. Clinical signs such as persistently impaired consciousness, a GCS score falling by 2 or more points, amnesia, focal deficits, and evidence of skull fracture all necessitate rapid triage.^{36–39} However, an increasing body of literature is starting to question the assumption that the severity of TBI must be tied to these classic signs⁴⁰ and have suggested that imaging and other factors may add specificity to predicting the need for interventions and outcomes.

56.4 Initial Resuscitation and Prehospital Stabilization

Once a child has sustained severe TBI, rapid assessment, stabilization with triage, and transfer to the highest-necessary level of care are the next steps. The centralization of pediatric trauma-specific resources is the natural extension of this axiom, which, along with patterns of resource allocation, are currently in search of validation. Olson and colleagues⁴¹ published one of the first studies to suggest that the centralization of resources, coupled with an urgency to transfer patients as quickly as possible, might be an incompletely developed model. Their historically controlled review found an increase in trauma-related deaths after the implementation of the Oregon State Trauma System. Patients injured in a rural setting were transferred to a higher level of care, incurring longer transport times. It appears that a system intended to facilitate rapid transfer may have resulted in premature transfer.

Table 56.1 The Glasgow Coma Scale score

	Original	Modified for infants
Best eye response	<ul style="list-style-type: none"> • Does not open eyes • Opens eyes to painful stimuli • Opens eyes to verbal command • Opens eyes spontaneously 	<ul style="list-style-type: none"> • None • To pain • To shout/loud noise • Spontaneously
Best verbal response	<ul style="list-style-type: none"> • No response • Incomprehensible sounds • Inappropriate words • Disoriented and converses • Fully oriented and converses 	<ul style="list-style-type: none"> • None • Grunt, agitated • Inconsolable screams • Consolable, cries • Smiles, coos
Best motor response	<ul style="list-style-type: none"> • No motor response • Extension (decerebrate posturing) • Flexion (decorticate posturing) • Withdraws purposefully from painful stimuli • Localizes painful stimuli • Follows verbal commands 	<ul style="list-style-type: none"> • None • Extension to pain (decerebrate posturing) • Flexion to pain (decorticate posturing) • Withdraws from pain • Localizes pain • Normal movement

Studies of transport decisions after severe TBI in children have been largely retrospective, reporting data on practice patterns. A prospective review of transport decisions comparing children who had severe TBI and were directly referred to an urban Level 1 pediatric trauma center with those who arrived by indirect referral⁴² demonstrated that those who had severe TBI (GCS score ≤ 8) and were directly referred had better survival. These limited data, along with information from adult TBI studies, allowed the first edition of the pediatric TBI guidelines¹⁹ to recommend the transfer of children with severe injuries to centers that had sufficient experience with such patients.

Regardless of transportation from the scene of the injury, several studies have consistently demonstrated increased morbidity and mortality due to failure to correct hypotension and hypoxemia or evacuate mass lesions.^{43–45} Gentleman reported during an 11-year period in England that an approximately eightfold increase in endotracheal intubation yielded a 64% reduction in hypoxic episodes.⁴⁶ This was accompanied by a 40% reduction in the mortality rate and a 45% increase in good outcome. Although the etiology of this improvement may be multifactorial, early, targeted intervention must be the objective of initial therapy.

The success of this study and others further reinforced the importance of reliable, early airway protection.⁴⁷ A provocative study by Gausche and colleagues,⁴⁸ however, added further clarity to the issue. In an RCT, airway management with bag valve mask (BVM) ventilation was compared with airway management with tracheal intubation in the prehospital setting in two urban pediatric trauma centers. There was no demonstrable advantage to tracheal intubation in the only prospective study to date. The severe TBI subgroup analysis (8 of 25 treated with BVM vs. 9 of 36 treated with tracheal intubation) showed that a “good” neurologic outcome was independent of how airway control was accomplished. The subgroup analysis suggests that aggressive airway management after severe TBI may not be essential. Further studies are needed to validate this potentially underpowered result and to address the question over a range of transport times.

The prehospital tracheal intubation of infants and children requires specialized training. There is currently little evidence that aggressive prehospital airway management changes the outcome for children or adults after severe TBI,⁴ and this topic is not explicitly addressed in the newest version of the guidelines.⁴⁹ All trauma patients with supraclavicular injury should be assumed to have cranial and cervical spine injuries until proven otherwise. The initial evaluation of a child after severe TBI begins with a demonstration by an experienced clinician that the child has a patent, maintainable airway. This, by definition, requires that the patient be conscious, alert, and breathing spontaneously. All unconscious patients are assumed to have an obstructed airway requiring immediate airway evaluation. (It will be helpful for readers if we define “unconscious” as not following commands, a Glasgow Coma Score of 8 or less, and not opening the eyes or speaking.)

The relatively larger head, occiput, and tongue of an infant, coupled with the shorter, narrower epiglottis, facilitate airway obstruction if the child’s sensorium has been clouded by a concussive injury. The rescuer must alleviate obstruction immediately (while protecting the cervical spine) to minimize secondary injury due to hypoxemia.

The mnemonic SOAP has been used for the necessary components of an optimal preparation to secure the airway.

- *S (suction)*. For most patients, a flexible 10F catheter will suffice. However, for school-aged children (older than 5 years), we recommend a rigid, plastic suction catheter that can remove particulate debris. This nonkinking catheter allows direct oropharyngeal suctioning. The suction device should be able to provide 30 L/min or greater and a vacuum of 300 mm Hg when clamped.
- *O (oxygen)*. Oxygen (FiO₂ = 1.0) should be delivered immediately to the patient before intubation. Optimal positioning of the patient requires that axial in-line immobilization be maintained to stabilize the cervical spine. The delivery of 100% oxygen facilitates the washout of nitrogen from the functional residual capacity, allowing adequate alveolar oxygenation for safe intubation of the trachea.
- *A (airway)*. Once the patient is properly positioned, ventilation and oxygenation are controlled, and an age-appropriate laryngoscope blade and endotracheal tube have been selected, the patient is ready to be intubated. Secure the endotracheal tube with adhesive tape, but refrain from passing the tape circumferentially around the neck because compression of the cerebral venous return may occur.
- *P (pharmacology)*. The medications chosen must be potent and rapid in their onset of action. The goals of analgesia, amnesia, and neuromuscular blockade must be met rapidly. Ideally, the patient never receives a preintubation positive-pressure breath.

Optimal tracheal intubation of the child with severe TBI requires a cerebroprotective, rapid-sequence induction technique whenever possible. BVM positive-pressure ventilation is to be avoided unless hypoxemia or impending herniation is suspected. One study⁵⁰ suggested that the BVM technique may cause more unintentional cervical spine manipulation than previously appreciated, so great care is advised during manual ventilation.

If a victim of head trauma meets any of the following criteria, assisted ventilation is indicated, with an orotracheal tube as the modality of choice:

- GCS score of 8 or lower
- Decrease in the GCS score of more than 3, independently of the initial GCS score
- Anisocoria of more than 1 mm
- Cervical spine injury compromising ventilation
- Apnea
- Hypercarbia (PaCO₂ > 45 mm Hg)
- Loss of pharyngeal reflex

In children, the recommended route of initial airway control is orotracheal intubation under direct vision.⁵¹ Nasotracheal intubation should be avoided in children with severe TBI for several reasons, including that blind passage of the endotracheal tube around the acute pediatric nasopharyngeal angle makes this procedure an unnecessary obstacle to rapid, physiologic resuscitation and risks injuring the underlying brain in cases of occult skull base fractures or sinus injuries. Orotracheal intubation can be accomplished with a two-person strategy that protects the cervical spine from injury. Although a normal lateral cervical spine roentgenogram is reassuring, it *does not rule out*

cervical spinal injury.⁵² Spinal immobilization must be maintained. One operator accomplishes this via in-line cervical immobilization while the second clinician intubates the trachea. Care must be taken during positioning in preparation for intubation in infants to avoid pressing into the soft tissues of the submental region and accompanying strap muscles because inadvertent airway obstruction will ensue.

56.4.1 Rapid-Sequence Induction

Tracheal intubation, although a life-saving procedure, remains a potent, noxious stimulus that can alter cerebral hemodynamics. Rapid-sequence induction safely secures the airway of an unprepared patient at risk for aspiration of gastric contents. There is minimal resistance to direct laryngoscopy, and the normal responses to having a large foreign body intentionally placed into the trachea are eliminated. Rapid-sequence induction has been repeatedly documented as a safer technique than either nasotracheal intubation or orotracheal intubation without neuromuscular blockade.^{53,54}

In the head-injured pediatric patient, a cerebroprotective rapid-sequence induction strategy should be employed. The sequence involves preparation, preoxygenation, sedation, neuromuscular blockade, and orotracheal intubation. Pharmacologic adjuncts are used to avoid the morbidity associated with hypotension, hypoxemia, intracranial hypertension, and gastric aspiration. The neurologic and hemodynamic status of the patient will direct the pharmacologic strategy. For the victim in cardiac arrest, cardiopulmonary resuscitation should begin immediately. No pharmacologic adjuncts are necessary to secure the airway. For the hemodynamically unstable patient, the combination of lidocaine, fentanyl, and vecuronium (► Table 56.2) is a safe and effective strategy. For the hemodynamically stable patient, the same sequence of drugs in addition to a rapidly acting benzodiazepine (midazolam) can be successfully used. Etomidate has become an effective agent for intubating the head-injured child. In hemodynamically stable patients, doses of 0.2 to 0.3 mg/kg reduce intracranial pressure (ICP) predictably while preserving the mean arterial pressure. Some reports have suggested an increased risk for adrenal insufficiency with etomidate in children with shock.^{55,56}

An alternative in the hemodynamically stable head-injured patient is thiopental, an ultrafast-acting thiobarbiturate. Thiopental reduces the cerebral metabolic rate for oxygen by 45 to 50% within 15 seconds of intravenous injection. This in turn attenuates the intracranial hypertension associated with direct laryngoscopy. The high lipophilicity of thiopental results in rapid cerebral wash-in and equally rapid washout. Therefore, although thiopental is an excellent agent for facilitating the rapid-sequence induction of anesthesia, it must be followed with another sedative–analgesic agent, although its availability in the United States has been limited in recent years. Fentanyl, a short-acting narcotic, and lidocaine reduce the catecholamine surge associated with direct laryngoscopy.

56.4.2 Circulatory Stabilization

The assessment of circulatory function after trauma involves a rapid determination of heart rate, blood pressure, central and

Table 56.2 Drugs for intubation of the head-injured child

Situation	Drugs
Cardiopulmonary arrest	Resuscitation drugs
Hemodynamically unstable	Etomidate, 0.1–0.2 mg/kg Fentanyl, 2–5 µg/kg
	Lidocaine, 1 mg/kg
	Vecuronium, 0.3 mg/kg
Hemodynamically stable	Etomidate, 0.3 mg/kg Fentanyl, 2–4 µg/kg
	Lidocaine, 1 mg/kg
	Diazepam or midazolam, 0.1–0.2 mg/kg
	Vecuronium, 0.3 mg/kg
Evidence of intracranial hypertension (and hemodynamically stable)	Etomidate, 0.1–0.2 mg/kg Fentanyl, 2–4 µg/kg Lidocaine, 1 mg/kg Thiopental, 4–5 mg/kg Vecuronium, 0.3 mg/kg

peripheral pulse quality, skin perfusion, and cerebral perfusion. The identification and correction of airway obstruction, inadequate ventilation, and shock take priority over a detailed neurologic assessment. The first priority in managing the head-injured patient is complete, rapid physiologic resuscitation. Hypoxemia and hypotension must be avoided during resuscitation.⁴³ Children who sustain age-specific hypotension (► Table 56.3) have a worse outcome in comparison with their normotensive peers.^{57,58} Mild systemic hypertension early after TBI may be beneficial and has been associated with favorable outcomes. Although intracranial hypertension and cerebral herniation are the major complications of severe TBI, brain-specific interventions in the absence of signs of herniation or other neurologic deterioration are not currently recommended. Moreover, interventions designed to manage malignant intracranial hypertension (e.g., osmotherapy or diuretics) may be counterproductive to initial resuscitative efforts.

Posttraumatic hypotension must be assumed to be hypovolemic (i.e., hemorrhagic) in nature, but it may also have a component of myocardial depression due to blunt cardiac injury. Blunt cardiac injury, however, is not as common in children as it is in adults.⁵⁹ Fluid therapy in hypovolemic shock is based on the principle of replacement of large volumes as rapidly as tolerated of whatever the patient is losing. The choice of which fluid to use has been a source of controversy. The current recommendation is 20 mL of isotonic crystalloid per kilogram given intravenously. Hypotonic fluid is to be avoided in the initial empiric resuscitation of the brain-injured patient. Subsequent doses of

Table 56.3 Age-specific hypotension

Age range (y)	Hypotension (mm Hg)
0–1	< 65
2–5	< 75
6–12	< 80
13–16	< 90

fluid should be more targeted based on the nature of fluid loss (i.e., packed red blood cells) and should be isotonic.

In summary, there is no Level 1 evidence to fully define optimal prehospital strategies. There is substantial evidence (generally categorized as Level 2 within the guidelines) to suggest that the administration of supplemental oxygen, avoidance of hypoxia and hypotension, early airway protection, and rapid fluid resuscitation are associated with improvements in outcome. Establishing a secure airway with sedative–analgesic agents and neuromuscular blockade and without causing secondary insults is essential in children who have severe injuries. The development of local emergency medical service and hospital evidenced-based protocols for achieving these goals is recommended, along with efforts to improve quality.

56.5 Diagnostic Studies

56.5.1 Computed Tomography

From its first moment of commercial availability in 1973, computed tomography (CT) has had an enormous beneficial impact on neurocritical care. A three-dimensional anatomical map of the brain structure facilitates diagnosis and management decisions in children with severe TBI. This modality, however, is not without limitations and must be utilized as one, albeit important, piece of information. After severe TBI, approximately 15% of adults with a normal CT scan will develop significant intracranial hypertension. Similarly, patients with normal initial CT scans but who have hypotension or abnormal posturing have the same propensity to develop intracranial hypertension as their counterparts with abnormal scans.^{60,61}

For children, there have been several recent advances in the field of imaging. Figg and colleagues found that repeated CT in children who did not have neurologic deterioration was not needed, leading to a new Level 3 recommendation within the guidelines.⁶² More provocatively, after studying a population of more than 40,000 children, Kuppermann and colleagues developed decision rules regarding when imaging is needed based on history and physical examination for children in the emergency department.⁶³ Importantly, this study was intended to limit the exposure of *uninjured children* to ionizing radiation, and it should not be extrapolated to children at high risk for severe injuries.

56.5.2 Monitoring of Cerebral Blood Flow

Techniques for the determination of cerebral blood flow monitoring after severe TBI include (1) stable xenon–enhanced CT, (2) radioactive (inhaled or injected) ¹³³Xe methods, and (3) transcranial Doppler methods.

Stable xenon CT cerebral blood flow measurement can aid in clinical decision making in the management of infants and children with severe TBI. This valuable technique was in clinical use but was temporarily removed from clinical use by the U.S. Food and Drug Administration (FDA). It is once again available as a research tool with investigational new drug (IND) approval by the FDA, but its use is very sporadic at this time. Although not a “monitor” in the sense that it does not provide a minute-to-minute assessment of changes, stable xenon CT blood flow measurement

provides important information about regional cerebral blood flow and its relationship to anatomical disturbances. This information can be readily coupled to nearly all CT scans obtained in the evaluation and follow-up of severely brain-injured infants and children, including the initial scan. The procedure can be completed in a relatively short time (usually within 30 minutes) and is technically contraindicated only if the FiO₂ or mean airway pressure is high (because of the need for the inhalation of 50% xenon gas, which has the effect of inherently increased density) or if the ICP is markedly increased. Serial stable xenon CT cerebral blood flow measurements can be coupled to a physiologic manipulation, such as altering the mean arterial blood pressure or PaCO₂. These dynamic “before and after” studies often provide additional insight into the optimal titration of bedside interventions and further prognostic information. In the largest series to date, we found that unfavorable outcome after severe TBI was associated with early decreases in cerebral blood flow to 20 mL/100 mg per minute or less and loss of CO₂ autoregulation measured with stable xenon CT imaging.⁶⁴ Although a promising modality, it has yet to make an impact on the routine care of children with severe TBI.

Obrist and colleagues⁶⁵ pioneered application of the ¹³³Xe method to assessment of patients after TBI. With multiple detectors, this method can provide information on regional cerebral blood flow and can be used in dynamic studies. Its advantages over the stable xenon CT method are that it can be frequently repeated, and it is a bedside technique. This method has been used in children with TBI to provide important descriptive information. However, its inability to correlate flow with anatomical disturbances is an important limitation.

Transcranial Doppler, a technique that uses sound waves to measure the blood flow velocity in intracerebral vessels, is frequently used to screen for vasospasm after spontaneous subarachnoid hemorrhage. In pediatric TBI, this modality has been used in several research applications to determine autoregulation, CO₂ reactivity, and hyperemia.^{66–68} Given its noninvasive nature, future research may expand the routine role of transcranial Doppler in pediatric TBI.

56.5.3 Monitoring of Cerebral Metabolism

The jugular venous saturation has been used extensively to monitor cerebral oxygen delivery in adults, and there has been recent interest in assessing its utility in children.⁶⁹ Studies in adults suggest that therapies like barbiturates and hyperventilation can be effectively titrated to jugular venous saturation. Gopinath et al reported the association of desaturation below the threshold value of 50% and mortality in adults.⁷⁰ Jugular venous desaturation below this level was rarely the sole indication that urgent intervention was necessary. Technical problems with placement and false desaturation readings are two additional caveats to this technique. Nevertheless, this monitoring tool can provide valuable information to assist in clinical decision making.

Furthermore, transcranial oximetry has been described as a noninvasive technique that may prove quite useful. Dunham and colleagues⁷¹ reported that measurement of the transcranial oxygen saturation (StcO₂) detected cerebral hypoxemia even in

the context of a cerebral perfusion pressure (CPP) of 70 mm Hg or higher in 16% of their nearly 4,000 observations over 6 days in a neurosurgical intensive care unit. Finally, brain tissue oxygen pressure (PbO₂) correlated with cerebral hypoperfusion, GCS score, severity of injury, and mortality. Further studies are needed to confidently and practically import these techniques to the bedside.

56.5.4 Monitoring of Intracranial Pressure and Brain Oxygen Pressure

It has long been recognized that clinical signs like pupillary size, light response, and papilledema fail as early indicators of intracranial hypertension. Most (but not all) patients at risk for the development of intracranial hypertension are identified by CT. ICP monitoring devices provide a window into the global pressure of the brain and impending crises—when the ICP reaches levels that can cause cerebral ischemia or herniation. ICP monitoring can be accomplished with either intraparenchymal or intraventricular devices. The preferred device remains the ventriculostomy catheter, which facilitates the real-time monitoring of ICP and affords the clinician the option of therapeutically draining cerebrospinal fluid (CSF). In the ideal circumstance, infection rates are acceptably low. Currently, ICP monitoring by ventricular catheter is considered the most accurate, inexpensive, and reliable method. The ventricular catheter also affords a key therapeutic option—CSF drainage. Other acceptable methods include parenchymal fiberoptic and microtransducer systems, whereas subarachnoid, subdural, and epidural monitors of any type are less reliable. Although the fiberoptic ICP catheter is useful in cases of severe intracranial hypertension with slit-like ventricles, data drift after 4 to 5 days may limit its use beyond the first week after injury.⁷² Furthermore, currently available fiberoptic catheters are single-calibration devices. Recently, an approach in which both an externalized ventricular drain (for drainage of CSF as a therapeutic maneuver) and an intraparenchymal device (for continuous measurement of ICP) are placed has been advocated.⁷³

Although there is currently insufficient evidence to support an absolute standard regarding when to place an ICP monitoring device, Level 3 evidence^{32,74–79} supports the placement of a device in patients with a GCS score of 8 or lower. ICP monitoring is considered a reasonable option for infants (even those with open fontanelles) and children with severe TBI and a GCS score of 8 or lower. The threshold of when to treat an elevation is currently any sustained ICP of 20 mm Hg or higher, again supported with Level 3 evidence.⁸⁰ Age-specific recommendations are currently not possible until our understanding of ICP, CPP, and the intricacies of cerebral hemodynamics are clarified in coming years. The range of 45 to 60 mm Hg currently represents the closest age-related goals for CPP.⁸¹ The identification of a “herniating pressure” and its relationship to both ICP and CPP remains critical to our understanding of this parameter. Moreover, the insidious nature of cerebral hypoxemia warrants the integration of multimodal measures of cerebral hemodynamics. ICP monitoring was also suggested to be appropriate in adults with severe TBI and a normal head CT scan if hypotension or motor posturing complicated the clinical course. This approach appears reasonable in children as well. The risks versus benefits

of ICP monitoring must be considered in the clinical decisions for patients in whom the complication rate is high, such as those with coagulopathy. Based on recent work with recombinant factor VIIa, this agent may rapidly minimize the risk for bleeding in patients with a coagulopathy after severe TBI.⁸²

Because of the high risk for cerebral hypoxia and/or ischemia,⁸³ the measurement of cerebral oxygen after TBI has garnered intense interest for some decades. Most recently, FDA-approved catheters that measure interstitial brain oxygen (partial pressure of brain oxygen, or PbO₂) have been introduced into the clinical milieu. Several reports have demonstrated some utility in PbO₂ monitoring.^{84–89} A report by Stiefel and colleagues showed that a protocol targeting a PbO₂ of at least 25 mm Hg decreased mortality compared with mortality in historical controls for adult TBI victims. In children, several studies suggest that PbO₂ monitoring may be helpful. Figaji and colleagues demonstrated that the maintenance of conventional management targets (ICP < 20 mm Hg, CPP ≥ 50 mm Hg, PaO₂ ≥ 60 mm Hg, SaO₂ ≥ 90%, and hemoglobin ≥ 8 g/dL) resulted in at least one episode of PbO₂ below 20 mm Hg in 80% of children and episodes of PbO₂ below 10 mm Hg in 32% of children,⁹⁰ and that children with these episodes had an increased incidence of unfavorable outcome in multivariate regression analysis. Steifel and colleagues demonstrated that decreased PbO₂ was associated with ICP and CPP derangements.⁹¹ A decisive study demonstrating that PbO₂ monitoring (or a PbO₂ threshold, more likely) improves neurologic outcome after pediatric TBI has yet to be performed. However, this technology, with relatively low risk and the potential to effect significant changes in clinical strategies, has been adopted within more centers over the last several years.

56.6 Medical Treatment of Elevated Intracranial Pressure

56.6.1 Hyperosmolar Therapy

Basic science support for the impact of osmotherapy is over a century old,⁹² with an ever-expanding variety of agents being introduced into the clinical armamentarium. First mannitol and then various hypertonic saline solutions have been considered an integral part of neurocritical care for pediatric TBI for years despite few definitive trials demonstrating efficacy in improving overall outcome. In fact, like many aspects of TBI care, mannitol administration is so ingrained within standards of care protocols that RCTs comparing mannitol with placebo are extremely difficult to design. It may be that other study designs, such as comparisons of established therapies based on comparative effectiveness research strategies, could play some role in establishing superior strategies. Pathophysiologically, the immediate benefit of osmotherapy in the context of raised ICP is undeniable; an immediate reduction in blood viscosity leads to decreases in cerebral blood volume and ICP via Poiseuille's law. This results in an immediate reduction in ICP, albeit a transient one. Muizelaar and colleagues⁹³ demonstrated that this mechanism (viscosity autoregulation) appears to operate only when pressure autoregulation of the cerebral blood flow is intact. When it is not intact, the decrease in viscosity will be accompanied by an increase in flow and no change in vessel caliber, cerebral

blood volume, or ICP. Note that if a bolus of mannitol is given too rapidly and produces transient systemic hypertension in a patient with defective pressure autoregulation, cerebral blood volume and ICP may transiently increase. More prolonged decreases in ICP are observed after the administration of mannitol and are related to the dehydration of brain parenchyma via an osmotic effect. Theoretically, this osmotic effect should operate only where the blood–brain barrier is intact, although there is some controversy regarding the location(s) of the dehydrating effect of mannitol.⁹⁴ It must be emphasized that osmolar therapy should be carefully titrated with careful attention to the maintenance of a euolemic state. Experimental evidence indicates that a high serum osmolarity (serum osmolarity > 320 mOsm/L) may be associated with renal failure in adults, thus limiting the use of mannitol under these conditions.

Hypertonic (3%) saline has become a popular alternative to mannitol, and an increasing body of literature supports its use to mitigate ICP crises. The start of this effort can be traced back to Peterson and colleagues,⁹⁵ who reviewed their experience with 68 children from 1985 to 1990. Their clinical protocol incorporated conventional therapy with intentional osmotherapy combining 3% saline infusion, furosemide, and mannitol. They showed effective ICP control for the majority of the patients, with no hyperosmolarity complications. Two studies using hypertonic saline solutions were judged to be Level 2 evidence in the most recent guidelines. Fisher and colleagues randomized 18 children to receive 3% normal saline solution or 0.9% normal saline solution to determine the effect of the intervention on ICP (> 2 hours after administration), ultimately finding that the experimental group had decreased ICP and a need for additional therapies.⁹⁶ Similarly, Simma and colleagues tested the hypothesis that 1.7% normal saline solution (administered as a continuous infusion over 3 days) would decrease ICP compared with lactated Ringer solution.⁹⁷ They failed to show an effect on overall ICP but did demonstrate a decreased need for other ICP therapies in the experimental group. Khanna and colleagues⁹⁸ reported their experience in 10 children with malignant intracranial hypertension refractory to conventional therapy. Doses ranging from 0.1 to 1.0 mEq of sodium per kilogram per hour were titrated to achieve a targeted serum sodium level. Targeted osmotherapy resulted in lower average ICP, increased CPP, less frequent ICP spikes, and predictable increases in serum sodium and osmolarity. One child required continuous venovenous hemofiltration. Over time, his renal function was fully restored. Larger, multicenter studies will shed additional insights regarding the optimal use of this treatment modality.

56.6.2 Hyperventilation

The vasoconstrictor effect of hyperventilation on the cerebral arteriolar system has been used in the management of patients with severe TBI for decades. However, contemporary management has veered away from the long-standing “blind” and prophylactic application of hyperventilation in the management of severe TBI. Studies in experimental models have demonstrated that the effects of hyperventilation on CSF pH and arteriolar diameter are short-lived (i.e., vessel caliber returns to baseline in less than 20 hours).⁹⁹ In addition, chronic hyperventilation produces a loss of metabolic (bicar-

bonate) buffer in the CSF, putting the cerebral circulation at greater risk because of hypersensitivity of the vasculature to changes in PaCO₂. Muizelaar and colleagues¹⁰⁰ compared mild versus moderate hyperventilation in adults after severe TBI, showing that moderate prophylactic hyperventilation (PaCO₂ = 26 to 27 mm Hg) was not beneficial and was associated with worse outcome at 3 and 6 months. These findings mirror reports demonstrating (1) early posttraumatic hypoperfusion after severe TBI, (2) widening of the arterial–jugular venous oxygen content difference that can be observed early after trauma; and (3) jugular desaturation that can accompany profound hypocarbia. It is important to recognize, however, that although the prophylactic application of hyperventilation can be detrimental, hypoventilation (leading to hypercarbia) is equally worrisome because of potential increases in cerebral blood flow leading to increased cerebral blood volume and intracranial hypertension. In summary, contemporary neurocritical care generally calls for mild hyperventilation to keep cerebral blood flow as normal as possible except in cases of impending herniation (in which hyperventilation to mitigate cerebral ischemia from brainstem compression can be lifesaving). It is likely that future studies demonstrating the feasibility of titrating cerebral blood flow—with serial measurements of CBF from stable xenon CT scan, extrapolated estimates of cerebral blood flow from PbO₂ monitoring, or continuous cerebral blood flow measurements from invasive devices—may show a role for hyperventilation in individual children after TBI.

56.6.3 Barbiturates

Barbiturates reduce ICP via a coupled reduction in the cerebral metabolic rate and cerebral blood flow, leading to a decrease in cerebral blood volume and ICP. As with other therapies, there have been no RCTs in children to test the efficacy of barbiturate therapy. Two small RCTs in adult TBI victims failed to demonstrate such an effect, but this should not be interpreted to mean that this therapy should not be considered. Goodman and colleagues¹⁰¹ reported an improvement in brain interstitial concentrations of lactate and glutamate accompanying a reduction of ICP in seven adults treated with barbiturates for refractory intracranial hypertension. Pittman and colleagues demonstrated that 52% of children responded to barbiturate therapy during refractory intracranial hypertension.¹⁰² Moreover, Kasoff and colleagues demonstrated that the use of barbiturates in children with TBI caused frequent bouts of hypotension, leading to the recommendation that the use of barbiturates be accompanied by invasive hemodynamic monitoring.⁷⁷ In addition to cardiovascular monitoring, it is recommended that electroencephalographic monitoring be used to assess the cerebral metabolic response to treatment, with the end point of this therapy generally being burst suppression. It is possible that as the use of hyperventilation wanes in the management of children with refractory intracranial hypertension, alternative therapies such as barbiturates will again be used.

56.6.4 Hypothermia

The theoretical benefits of therapeutic hypothermia have been under study for decades; mechanisms like decreased metabolic

demand leading to decreased cerebral blood flow and cerebral blood volume with decreased ICP, alterations in cell death pathways, decreased intracranial hypertension, and others have been postulated. Over time, numerous anecdotal cases and uncontrolled trials have suggested favorable and unfavorable effects. Until very recently, controlled trials of the use of therapeutic hypothermia in human head injury were lacking.

Experimental models of cerebral ischemia and trauma suggest that transient, mild, or moderate hypothermia (32 to 34°C) attenuates excitotoxic neurotransmitter concentrations and the local proinflammatory cytokine response, thereby producing beneficial effects on neuronal recovery and neurologic outcome.¹⁰³⁻¹⁰⁵ Efficacy for hypothermia was demonstrated in adults after cardiac arrest in 2002, spurring interest in extending this therapy to other brain injuries.^{106,107} For adults with TBI, hypothermia has had mixed results. Two RCTs (32°C for 24 or 48 hours) have shown beneficial effects,^{108,109} with decreased seizure frequency, decreased ICP, and transient improvements in outcomes (especially in subjects with admission GCS scores of 5 to 7). A larger, multicenter trial, however, was unable to reproduce the single-center experience.¹¹⁰

In pediatric TBI, a large RCT was performed to test the efficacy of early hypothermia in improving overall outcome.¹¹¹ In this most important study, 225 children were randomized to receive hypothermia (32 to 34°C) or normothermia within 8 hours, were maintained at that temperature for 24 hours, and were rewarmed over approximately 16 hours. No beneficial effect was observed in the hypothermia group regarding outcome, with a trend toward increased mortality and decreased functional outcome (Pediatric Cerebral Performance Category Scale score at 6 months) despite hypothermia leading to improvements in ICP. Several potential confounders were noted within the study (the normothermia group received greater amounts of hyperosmolar therapies, both groups had substantial amounts of hyperventilation). Nevertheless, this study has questioned the utility of hypothermia as applied to all children with severe TBI, leading to questions of whether there are specific populations of children that might benefit from hypothermia.

56.7 Surgical Treatment of Elevated Intracranial Pressure: Decompressive Craniectomy

One of the more controversial areas in the management of both adults and children with refractory intracranial hypertension is the use of decompressive craniectomy. Controlled studies of this modality are lacking in adults and children. Described by Cushing in 1905,¹¹² there has been a resurgence of interest in this approach sparked by laboratory studies and several recent case reports suggesting that decompressive craniectomy may result in ICP reduction and a good outcome in selected patients with intracranial hypertension refractory to medical therapy.¹¹³ Although some have reported disappointing results,^{114,115} De Luca and colleagues reviewed 22 cases and reported with guarded optimism that selected patients may benefit.¹¹⁶ Taylor and colleagues¹¹⁷ showed positive results with very early (within 30 hours of injury) decompressive craniectomy for children

with intracranial hypertension despite optimal management. The marked reduction in postoperative ICP was deemed the primary neuroprotective outcome in this prospective trial. The common thread in all trials that show positive outcomes are young age (younger than 16 years) and early decompression (within 30 hours of injury). The variable outcomes in the collectively published reports underscore the need for a multicenter RCTs to address the question with a larger sample size. More clarity is needed to determine optimal timing, unilateral versus bilateral craniectomy, and the effect of comorbidities on outcomes. Specific recommendations or guidelines for this procedure cannot be made, and like other second-tier therapies for refractory intracranial hypertension (barbiturates, hypothermia, induced hypertension), decompressive craniectomy is used with varying frequency depending on local experience and the discretion of the management team. A seminal study for decompressive craniectomy in adult TBI victims was recently completed, ultimately randomizing 155 adults with severe diffuse TBI.¹¹⁸ Despite successfully alleviating intracranial hypertension, the surgical group unexpectedly had an increased rate of unfavorable outcomes (odds ratio=1.84 [1.05 - 3.24], $p=0.03$). Technical considerations, patient selection criteria, and differences in medical therapies between groups have all been hypothesized as causes for this curious finding.

56.8 Treatment in the Neurocritical Care Unit

Once the initial resuscitation is completed and evacuable intracranial masses have been addressed, the maintenance of physiologic stability and the recognition and management of intracranial hypertension are the priorities. The injured brain has complex metabolic requirements that are poorly understood. Autoregulation of blood flow may be disturbed, and metabolic demands may be either decreased or increased. It is clear, however, that evidence of neuronal death from cerebral ischemia is a common autopsy finding in patients who die after severe TBI. Maintenance of an adequate CPP is the current therapeutic approach that appears to minimize the risk for the development of secondary ischemia. Assessment of the effect of manipulating CPP on cerebral blood flow or other multimodal markers of cerebral metabolism can provide valuable information and aid in the titration of care. Monitoring of the central venous pressure is essential, and assessment of the cardiac output can be valuable in selected cases. The titration of vasopressor or inotropic support may be needed once adequate filling pressure and hemoglobin are confirmed. In some situations, such as the development of neurogenic pulmonary edema, the optimal titration of cardiopulmonary support can be a formidable challenge and a key determinant of outcome. In addition to the importance of CPP, the selection of an optimal threshold for ICP may play a role. Adult victims of severe TBI with an ICP above 20 mm Hg have a poorer outcome than those without increased ICP. Although a large prospective RCT of patients with and without both ICP monitoring and CPP-targeted management has not been performed, a prospective cohort study by Ghajar and colleagues suggested better outcome in adults monitored and treated with CSF drainage than in those without ICP monitoring.¹¹⁹ Several studies have suggested that optimal outcome is

achieved if the neurointensivist responds to even modest levels of intracranial hypertension (i.e., ICP > 15 mm Hg). Further study is needed, particularly in infants and children.

56.8.1 Sedation Analgesia and Neuromuscular Blockade

Sedation and neuromuscular blockade should be used in the setting of intracranial hypertension once appropriate monitoring has been established. Often, in the initial resuscitation, sedation must be carefully titrated. It is difficult to maintain the balance that allows cardiovascular stability, analgesia, and anxiolysis during transport and initial CT yet allows rapid emergence for clinical assessment when a decision regarding surgery or intensive care management may be necessary. Narcotics, benzodiazepines, or small doses of barbiturates are generally recommended for routine use. Recently, for adults, the use of propofol, a nonbarbiturate intravenous anesthetic, has migrated out of the operating theater into the intensive care unit. The utility of propofol in the rapid induction of anesthesia (it works as quickly as thiopental) is surpassed only by its facility in emergence.¹²⁰ The rapid emergence from sedation with minimal confusion has allowed adult neurointensivists to use propofol preferentially over thiobarbiturates and benzodiazepines for sedation after severe TBI. However, reports in the mid-1990s of an idiosyncratic, lethal propofol infusion syndrome led to the re-evaluation of the role of this general anesthetic in the pediatric intensive care unit.^{121–124} Subsequently, propofol infusion syndrome in the deaths of several adults has also been reported.^{125–128} Based on recent recommendations of the FDA, propofol cannot be recommended as a continuous infusion for the sedation of infants and children with severe TBI (www.fda.gov/cder/pediatric/labchange.htm).

Although neuromuscular blockade has been used commonly in the United States, there has been interest in recent years to more clearly define its indications, duration of therapy, and monitoring. It is currently recommended to use neuromuscular blockade after failure to control ICP with optimized mechanical ventilation, sedation, head position, and temperature control. Once neuromuscular blockade is employed, care must be taken to allow therapeutic monitoring with train-of-four testing as well as daily drug holidays.

To our knowledge, no controlled trial of various sedation regimens has been performed in patients with severe TBI. In contrast, Hsiang and colleagues¹²⁹ studied 514 adults with severe TBI and suggested that *prophylactic* neuromuscular blockade was associated with increased length of intensive care unit stay and nosocomial pneumonia. As with most therapies in this setting, careful assessment of indication and meticulous titration of therapy are essential. Finally, intermittent doses of thiopental and/or lidocaine are often needed to blunt excessive rises in ICP secondary to routine patient care maneuvers, such as suctioning.

56.8.2 Cerebrospinal Fluid Drainage

Drainage of the CSF is a direct method to reduce ICP with minimal risks (other than the obvious risk of inserting the ventricular catheter). However, despite widespread use,

studies of the effect of CSF drainage on CPP, cerebral blood flow, and neurologic outcome have been limited, particularly in children. Shapiro and Marmarou described the utility of CSF diversion in 22 children in an observational study, reporting that more than 75% of children observed demonstrated decreased ICP and increased brain compliance (measured with the pressure–volume index) after CSF drainage via an externalized drain.⁷⁹ Fortune and colleagues¹³⁰ compared the effect of ventriculostomy drainage and mannitol in adults after severe TBI and observed similar effects on cerebral blood flow and ICP. CSF drainage was associated with a greater increase in jugular venous saturation than mannitol administration. CSF can be drained intermittently or continuously in children, with threshold values for drainage determined based on the clinical indication. Interestingly, Shore and colleagues¹³¹ suggested that continuous CSF drainage was associated with lower concentrations of a large number of biochemical mediators of secondary injury, such as cytokines, in comparison with intermittent drainage. In addition, a lower ICP was seen with continuous rather than with intermittent drainage. Further study is needed.

56.9 Controversial Issues

56.9.1 Head Position

Head position has been an area of great controversy. Feldman and colleagues¹³² conducted a prospective randomized study of the effect of head position on ICP, CPP, and cerebral blood flow in 22 patients after severe TBI. Both the ICP and the mean carotid pressure were significantly reduced in the 30-degree position compared with the 0-degree position. There was no change in CPP or flow with this intervention. Thus, in general, raising the head to the 30-degree position reduces ICP without deleterious effects on CPP and is preferred. Head elevation and midline position improve jugular venous drainage and possibly CSF drainage and decrease the contribution of these components to ICP, but the effect overall is not dramatic.

56.9.2 Controlled Hypertension

Another controversial area in management relates to the use of induced hypertension to control refractory intracranial hypertension. Whether pressure autoregulation of the cerebral blood flow is intact or defective, hypotension or an inadequate CPP must be rigorously avoided. If pressure autoregulation is impaired, cerebral blood flow is directly related to CPP, and hypotension directly reduces flow. If pressure autoregulation is intact, as CPP is reduced, reflex cerebral vasodilation occurs (to maintain flow), which increases cerebral blood volume and ICP. Note that this latter phenomenon occurs as CPP is reduced within the autoregulatory range.

Based on measurements of blood flow and jugular venous saturation in adults with severe TBI, an optimal perfusion pressure threshold of 60 to 70 mm Hg is generally observed. Currently, a CPP of 50 to 60 mm Hg is the goal for infants younger than 2 years. Based on the relationship between CPP, vessel diameter, cerebral blood volume, and ICP, in selected patients with refractory intracranial hypertension, the induction of arterial hypertension (CPP increased to between 100 and 140 mm

Hg via the infusion of phenylephrine) reduces ICP. However, hypertension reduces ICP only when the pressure autoregulation of cerebral blood flow is intact because it is a hypertension-mediated reduction in vessel caliber that produces the reduction in cerebral blood volume (to maintain a constant flow) and resultant reduction in ICP. In addition, it is unclear what the short- and long-term effects of the applied hypertension are on the development of cerebral edema because the greater hydrostatic pressure applied could exacerbate edema formation. The optimal management of blood pressure after severe TBI requires both extensive monitoring of the involved factors and an in-depth understanding of the mechanisms at work. Induced hypertension is not recommended except as a second-tier therapy and only with careful monitoring. Unfortunately, the use of this intervention is even more complex in the management of infants and children after severe TBI because a single general threshold value of CPP for adequate perfusion is not applicable. Downard and colleagues⁸⁰ have suggested a minimal value of 40 mm Hg for children. In their report of nearly 200 children with severe TBI, all children with a mean CPP of less than 40 mm Hg died. One would anticipate that this value is directly related to age; however, the relationship has not been defined. Management must be tailored to, and carefully titrated in, each individual patient.

56.9.3 Additional Treatment Issues

Seizures are quite common after TBI and should be aggressively treated to prevent complications related to increased metabolic demand during periods of tenuous cerebral blood flow. However, there is little evidence to suggest that the administration of antiepileptic agents prevents the long-term development of epilepsy. Lewis and colleagues found that the administration of phenytoin led to decreased seizure frequency early after TBI in a small series, ultimately judged to be Level 3 evidence.¹³³

Careful attention must be paid to the serum sodium concentration. An increasing body of literature has developed suggesting the harm that may occur if hyponatremia develops in the acute phase of injury. For this reason, children should generally receive isotonic solutions. If hyponatremia develops, it can be attributed to either syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting.^{134,135} Care should be taken to determine the cause of hyponatremia correctly because the management of SIADH involves fluid restriction, whereas that of cerebral salt wasting involves the administration of isotonic or hypertonic saline.

The provision of adequate calories and protein is essential during the catabolic response to critical illness, and the beneficial effects of early feeding (either enteral or parenteral) in the critically ill or injured patient are well described. In adult TBI victims, increased administration of calories within the first 7 days was associated with improved outcome in a large cohort study from New York State,¹³⁶ yet similar hypotheses have not been adequately tested in children. In children, an immune-enhanced diet was tested in a small RCT, yet this failed to demonstrate meaningful benefits.¹³⁷ Moreover, the management of glucose administration has received significant attention in the past several years, with several studies demonstrating a relationship between hyperglycemia and poor outcome.^{138,139} It is

still unclear if treating hyperglycemia would alter this relationship, but it appears obvious at this time that care must be taken to monitor the serum glucose closely after TBI.

Finally, glucocorticoids are not recommended in the treatment of patients with severe TBI unless catecholamine-refractory shock develops. Pituitary stalk injury has been reported after severe TBI and can complicate it.¹⁴⁰⁻¹⁴² When corticosteroids are used, a serum cortisol level should be obtained before the treatment dose is administered. This pretreatment level is used to inform the decision to continue therapy.

56.10 Summary

The optimal care of an infant or child with severe TBI requires a multidisciplinary approach in each phase of management. A prompt and vigorous resuscitation including the stabilization and control of ventilation is essential. After the initial evaluation and necessary surgical intervention, multimodal monitoring and the carefully titrated management of intracranial hypertension are recommended to optimize cerebral perfusion, facilitate metabolic homeostasis, and minimize cerebral swelling. Meticulous and optimal neurocritical care management will be the basis for the delivery of future targeted therapies as additional information becomes available on the biochemical aspects of the evolution of secondary neuronal damage and repair.

Pearls

- Management of the pediatric patient following trauma brain injury provides unique challenges due to differences in the basic neurobiology, primary and secondary mechanisms of injury
- The guidelines and common data elements effort provide an overview of our present knowledge base and gap as well as the opportunities for improved communication of future studies and the ability to compare and collate clinical studies going forward.
- Multidisciplinary neurocritical care teams are recommended for the optimal management of these complex often multi-trauma patients for the rapid assessment and rapid institution of treatment
- The goal of acute care management of the brain injured child is to optimize the environment for recovery including perfusion, metabolic homeostasis, neurophysiology, and reparative mechanisms.
- While intracranial pressure monitoring in and of itself is insufficient as a sole therapeutic target, ICP monitors should be considered and placed for any child with a GCS < 8 to assist in the overall management of these patients and treat for any sustained ICP > 20 mmHg
- While available, other types of neuromonitoring are often under-utilized though their addition (i.e.) brain tissue oxygen monitoring, provides an opportunity for a richer understanding of the response of the brain in the acute setting
- Improved understanding of the complex pathophysiology as well as the reparative physiology of the injured brain will lead to further development of new therapeutic options.

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57 Rehabilitation and Outcome of Head Injuries

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Traumatic injury is the leading cause of death in children and adolescents,^{1,2} and pediatric traumatic brain injury (TBI) accounts for approximately 40 to 50% of injury deaths.³ Despite efforts at prevention, pediatric head injury remains a significant public health problem in the United States. Of children who survive severe head injury, 50% experience neurologic deficits affecting multiple areas of function.⁴ Although pediatric brain injury was once considered more benign than injury during adulthood,⁵ studies indicate that younger children may be more at risk for impairment than older children, particularly if the head injury is severe.^{6,7} Thus, it is easy to understand why research on the outcome and rehabilitation of children with brain injury continues to receive a great deal of attention by a variety of health care professionals.

57.1 General Considerations Affecting Outcome

57.1.1 Severity of Injury

Not surprisingly, evidence clearly indicates that children sustaining severe injuries have the worst prognosis. Many of these children exhibit long-term deficits in a number of cognitive, psychosocial, and adaptive domains.^{8,9} A unique study of adults who were injured during their preschool years demonstrates the far-reaching effects of severe injury incurred in early childhood.¹⁰ Of the 39 children followed to adulthood, 15 required special school placements for either physical (21%) or mental (18%) disabilities. Despite the fact that the remaining 59% attended “typical” schools and more than two-thirds of this group demonstrated a low-normal or higher IQ, only 23% were able to work full time. This finding suggests that either personality changes or behavior problems, or both, interfered with their functioning as adults. Other studies have indicated that individuals sustaining moderate to severe injuries are more likely to exhibit long-term reductions in quality of life and deficits in a broad range of social skills.^{9,11}

57.1.2 Preexisting Conditions

Although the information on this topic is somewhat limited, a study by Donders and Strom¹² indicated that children with preexisting learning disabilities exhibited a greater than expected drop in intellectual functioning following a moderate to severe head injury when compared with a group that had no history of preexisting learning difficulties. Another case series, by Schmidt and colleagues,¹³ indicated that children with a history of low birth weight demonstrated an attenuated pattern of recovery in terms of verbal memory, academic performance, and adaptive skills when compared with a control group of normal birth weight matched for age, sex, injury severity, and socioeconomic status. Importantly, these groups demonstrated very similar patterns of test performance at baseline, and differences emerged only over time, suggesting a difference in the trajectory of

recovery rather than a preexisting difference in performance between the two groups.

57.1.3 Age of the Child

Current conceptualizations of pediatric head injury suggest that younger age at injury is associated with a less favorable prognosis. In light of this new understanding of the developmental consequences of TBI in children, it is particularly important to consider age at injury in the discussion of outcome. For example, findings from a longitudinal study of very young children (i.e., 4 months to 7 years old at the time of injury) demonstrated not only minimal recovery 6 months after injury but also a reduction in the acquisition of new skills after severe injury.¹⁴ Another study of children ranging in age from 2½ to 16 years at the time of injury found older age at injury predicts better adaptive function for up to 5 years after injury, particularly in the absence of premorbid learning problems.¹⁵ These findings highlight important differences between adult and child outcome research. In children, injury occurs to a developing brain. Thus, Taylor and Alden strongly recommend that the age-related effects of injury and subsequent recovery be investigated with consideration of age at injury, time since the insult, and age at testing. Age and time since insult may take on even more significance when the neuropsychiatric symptoms associated with injury to the frontal systems, such as those commonly seen in children with moderate to severe injury,^{16,17} are the focus of investigation. For example, Levin et al found that younger and older children with *similar* levels of severity and times since injury showed *different* patterns of executive deficits. The differences in injury pattern and recovery of function might be accounted for, at least in part, by the developmental stage of the brain at the time of insult.

57.1.4 Resources of the Family

A child's recovery from head injury may be affected by both neuropsychiatric (e.g., Glasgow Coma Scale [GCS] score, duration of loss of consciousness, de novo psychiatric problems, neurologic status) and what Max et al¹⁸ termed the psychosocial disadvantage factor (e.g., family dysfunction, family psychiatric history, lower socioeconomic status). Noting the adverse impact of pediatric TBI on families, Wade et al,¹⁶ Taylor et al, and Yeates et al completed a series of studies that demonstrated the complicated interactions between premorbid and postinjury family functioning and outcome after TBI in school-aged children.^{19–23} In their 1997 study, this research group showed that perceived family burden and psychological distress are related to recovery in children with head injury.²⁰ Family function before the traumatic injury influenced both behavior and cognitive outcome. These findings were extended in 2004 with a controlled study that was one of the first to demonstrate the importance of family environment in the postacute period. Based on their previous finding indicating the influence of preinjury family function on later recovery, the investigators

controlled for family factors when they assessed outcome. Measures of postinjury family environment (i.e., family economic burden, parental psychological distress, and family dysfunction) were associated with 1-year outcome, with behavior and school function most affected in severely injured children. Further studies by this group have found that the family system continues to influence recovery from brain injury for as long as 4 years after injury.^{21–23} Less than optimal family circumstances exacerbated the adverse effects of TBI on overall behavior, social outcome, and academic skills, but not on cognitive status as measured by neuropsychological tests. However, a series of more recent investigations by Schmidt and colleagues indicates that family socioeconomic status, especially a family's access to financial resources, influences a child's trajectory of recovery in tasks of basic emotion processing.^{24,25} Interestingly, these investigators also demonstrated that many of these effects were more significant in younger children.

The research regarding the influence of family function is not equivocal. Others suggest that the family disorganization frequently noted after pediatric head injury is not necessarily related to dysfunction that was present before the injury occurred.²⁶ Schwartz et al²⁷ investigated the relationship between behavior problems and family function 4 years after injury. Children with TBI who met the criteria for clinically significant postinjury behavior problems were compared with children who had head injury and displayed no such problems. This comparison indicated that although the clinically involved children were more socially disadvantaged, family dysfunction developed only late in the recovery course. Comparison groups did not differ at either preinjury or early (i.e., within the first year after injury) time points, a finding suggesting that negative family outcomes emerged after the head injury.

57.1.5 Mild Injuries

Of the more than 1 million TBIs that occur each year in the United States, mild TBIs are by far the most common, representing at least 79% of all TBIs.²⁸ In recent years, there have been growing concerns regarding the consequences of very mild head injuries (i.e., concussions).²⁹ Concerns have been most notable regarding repetitive mild injuries. Although research continues on the long-term sequelae of these repeated concussive events, some initial data suggest that individuals sustaining three or more mild concussions exhibit long-term decreases in verbal memory skills.³⁰ As many of these mild injuries occur during the course of athletic competition, a major focus of clinical management in these cases is determining when an athlete should return to play. The use of computerized testing for baseline measurement of an athlete's neurocognitive abilities, followed by regularly repeated assessments after a concussion, has gained popularity as a way of guiding and making more informed decisions regarding return to play.^{31–33} Although the use of computerized testing as a sole means of making these decisions has not been universally accepted (see Echemendia et al³⁴ and Mayers and Redick³⁵), it remains a common practice. A major concern with relying exclusively on computerized baseline testing to inform return-to-play decisions is the concern that athletes may attempt to invalidate their baseline performance by intentionally "faking bad" during these evaluations. There is some evidence to suggest that postinjury computerized

batteries, if interpreted with regard to population-based means (as opposed to baseline scores), may continue to provide a valid assessment of postconcussive cognitive symptoms.^{34,36}

57.2 Assessing Neurobehavioral Consequences in the Acute Period

Comprehensive neuropsychological testing is rarely completed in the inpatient setting because the acute consequences of TBI obscure the accuracy of measurement as a consequence of baseline effects. One important exception might be the application of the Children's Orientation and Amnesia Test (COAT),³⁷ a standardized assessment of posttraumatic amnesia. The COAT can be administered serially and is an appropriate component of any inpatient evaluation conducted following a pediatric TBI. Posttraumatic amnesia has been found to be a potent predictor of later recovery from TBI and as such provides useful information for both the neurosurgeon and other rehabilitation providers.

57.2.1 Functional Skills

Assessing functional living (i.e., adaptive skills) following a mild or moderate injury is an important aspect of monitoring recovery, guiding return to play in the case of sports-related injuries or return to school in the case of other, more serious injuries, and helping both clinicians and parents understand when more in-depth evaluation is necessary. Adaptive abilities are those needed to function independently at an age-appropriate level.³⁸ A current challenge in the outcome field is to develop appropriate measures of functional outcome for children. Adaptive abilities or functional outcome in the broadest sense is frequently measured with the Glasgow Outcome Scale (GOS).³⁹ In children, the GOS score depends on return to school as a measure of successful outcome. A child's return to school, however, does not have the same significance as an adult's return to work because legal mandates require schools to attempt to educate all children.⁴⁰ In addition, the broad GOS categories lack sensitivity,⁴¹ particularly when used in a pediatric population, because they fail to consider how the demands on children change across different developmental levels.

A revised version of the GOS, the GOS-Extended (GOS-E),⁴² has promise for evaluating outcomes in pediatric populations but lacks developmental specificity. In a recent study, Beers and colleagues⁴³ modified the GOS-E to create a more developmentally appropriate measure, the GOS-E Pediatric Version (GOS-E Peds). These investigators reported that the GOS-E Peds had good predictive, criterion, and discriminant validity at 3 and 6 months within a sample of children sustaining mild to severe TBIs. The authors argued that the GOS-E Peds would be an appropriate measure to use in future studies assessing outcomes following pediatric head injuries, although few studies have employed this measure to date.

Although not without problems, a more sensitive indicator than the GOS of adaptive competence in children is the Vineland Adaptive Behavior Scales (VABS).⁴⁴ This norm-referenced instrument has the advantage of using a semistructured interview with the parent to measure adaptive skills across the domains of communication, daily living, and social domains and

appears to be sensitive to the changes associated with TBI.⁴⁵ Using serial VABS data, Fletcher et al⁴⁶ showed that age-specific adaptive behavior declined in the year following severe head injury but not after mild to moderate injury. Levin et al⁴⁷ found that functional outcome on the VABS was inversely related to the depth of a brain lesion on magnetic resonance (MR) imaging at follow-up. The VABS is also useful for evaluating premorbid function, particularly in younger children,⁴⁸ and in assessing isolated aspects of adaptive behavior, such as socialization, in the later recovery period. A recent study by Rivara et al⁴⁹ in which the VABS was used indicated that children with moderate or severe TBI exhibited decreases in the ability to participate in age-appropriate activities, communication, and self-care skills, none of which returned to baseline levels at 24 months after injury. Interestingly, these investigators also observed decreases in quality of life at 2 years after injury in children sustaining a complicated mild TBI (i.e., a mild injury with evidence of findings on neuroimaging), suggesting that, at least in some individuals, these injuries may not be as benign as suspected. Other evidence indicates that injury severity and preinjury factors, such as behavioral functioning, adaptive skills, and family environment, can play a role in long-term functional outcomes, even more than 10 years after injury.⁵⁰⁻⁵³

57.3 Neuropsychiatric Manifestations during the Period of Active Recovery

Some of the most common neurobehavioral sequelae within the period of active recovery (i.e., the initial 2 years after injury) from closed head injuries involve deficits in processing speed, memory (especially working memory), behavior regulation, and attention. These difficulties can result in significant behavioral disruption, difficulties in returning to grade-level academic work, and problems with activities of daily living. If deficits in neurocognitive functioning are still evident after the initial postacute period (i.e., the period following the resolution of posttraumatic amnesia and following participation in intensive inpatient or outpatient rehabilitation), referral to a pediatric neuropsychologist for a comprehensive evaluation of cognitive domains is recommended. Specifically, this assessment should be completed before a child resumes full-time academic work. Although a pediatric neuropsychological evaluation is most critical for children who sustained a severe injury, often children with moderate injuries who recover relatively quickly and who typically have little or no need for long-term rehabilitation can also benefit from this kind of thorough postinjury assessment. There are several important factors to consider before a referral for a pediatric neuropsychological evaluation:

- Can the child reliably respond to simple commands and complete basic motor tasks when asked to do so?
- Does the child have sufficient energy to sustain attention and effort for at least 2 to 3 hours of testing?
- Are the child's language and motor skills sufficiently recovered so as to make testing within these domains possible and interpretable? Of note, although continued deficits in either or both of these domains do not explicitly rule out the possibility of neuropsychological testing, deficits do

suggest that referrals should be made to practitioners with specialized experience and training in the assessment of postacute pediatric TBI.

57.4 Areas of Comprehensive Assessment

A comprehensive neuropsychological evaluation involves assessment across neurocognitive domains, including intellectual ability, academic skills, receptive and expressive language skills, visual and verbal memory skills, visual-motor and fine-motor deficits, behavioral and emotional functioning, and attention and executive skills.

Intellectual testing is an important component of pediatric neuropsychological evaluations because it establishes a child's current abilities and provides a baseline level of performance, which is useful in tracking a child's development as he or she matures and as moves farther and farther away from the actual injury. Academic skills are also an important component of an assessment because these skills are frequently robust and may be more resistant to deterioration following a severe injury. As a result, academic performance can help to estimate a child's premorbid abilities. Importantly, because children are continuing to acquire new academic skills, they remain at long-term risk for significant academic delays secondary to a failure to make developmentally appropriate progress. Findings in these two areas are often elaborated on by the identification of a child's strengths, and weaknesses in the cognitive domains discussed in the subsequent sections.

Language skills can be divided into receptive (i.e., the understanding of language) and expressive (i.e., the use of language) skills. Both types of assessment should be conducted in a thorough evaluation in order to determine if additional referrals for outpatient speech and language therapy services are necessary. Language assessment is also an important component of a pediatric neuropsychological evaluation because difficulties with language can often contribute to or exacerbate behavioral and social deficits.

Memory problems, especially difficulties with working memory, are some of the most common problems following a closed head injury. Working memory is the ability to keep information in mind and use it for a specific purpose. For example, working memory is required when someone gives you directions on how to get to a specific room in a building you have never visited before. Because working memory is mediated by structures within the frontal lobe, specifically the left dorsal-lateral prefrontal cortex, it is extremely vulnerable to TBI. Deficits in working memory can lead to problems with everyday behaviors, such as compliance with medication. Although working memory problems are common after TBI, long-term verbal and visual memory difficulties can also arise because these functions are largely mediated by temporal structures, such as the hippocampus, which are structurally and metabolically vulnerable.

Problems with processing speed and motor control are frequent following pediatric TBI. Deficits in these domains can lead to problems in efficiently carrying out academic and adaptive tasks. Measures of processing speed are some of the most sensitive to neurologic dysfunction and should be incorporated in any thorough assessment of neurocognitive skills.

Executive deficits are also very common following pediatric TBI and are related to many of the behavioral difficulties discussed below. Executive functions are a wide range of neuro-cognitive skills and include the following: initiation of activity (i.e., the ability to begin meaningful motor or cognitive tasks); sustaining (i.e., the ability to persist in cognitive or motor tasks that have been initiated); shifting (i.e., the ability to change focus when necessary in order to change strategy or carry out another procedure); and inhibiting (i.e., the ability to withhold a response and/or regulate action as is appropriate for the situation). Because many of these abilities are mediated through structures in the frontal lobes, they are exceptionally vulnerable to closed head injuries. Moreover, because of their protracted development, children may not fully express the extent of the damage they have sustained until the demands on these skills increase as they grow older.

Although traumatic head injury often results in physical impairment, more problematic consequences involve the individual's cognition, emotional function, and behavior. These cognitive, emotional, and psychosocial deficits are frequently referred to as the neuropsychiatric sequelae of brain injury and are a significant cause of disability. Personality and behavior changes following closed head injuries are common manifestations of moderate and severe injuries. Often, these changes in behavioral functioning result in a diagnosis of a novel-onset psychiatric disorder. In a series of investigations, Max and colleagues⁵⁴⁻⁵⁶ demonstrated that upward of 45% of all children sustaining a TBI exhibited novel-onset psychiatric disorders at 3 months after injury. Furthermore, these investigators showed that from 60 to 80% of children sustaining a severe TBI exhibited signs of novel-onset psychiatric disorders.^{54,56} Max et al also suggested that severity of injury, lifetime psychiatric disorder, family psychiatric history, preinjury family function, socioeconomic status, and preinjury intellectual function contributed to, but could not account for, the increase in novel psychiatric diagnoses following injury. A recent follow-up to these initial investigations indicated that nearly half of all children sustaining a TBI exhibited a novel-onset psychiatric diagnosis at 3 months after injury and that personality change and externalizing disorders occurred significantly more frequently in the TBI group than in the orthopedic control group.

57.5 Late Effects of Pediatric Traumatic Brain Injury

As the devastating consequences of TBI in childhood have become better understood, more studies have undertaken what has become known as research into the late effects of TBI. This body of research provides important information for neurosurgeons because it informs them regarding the cognitive prognosis after TBI. This is particularly important for children, who by definition will continue to engage in challenging cognitive pursuits for years after injury. It has been our experience that neurosurgeons, who provide the first line of treatment after TBI, are sought out by families for treatment recommendations sometimes years after the acute injury period, when heretofore unappreciated cognitive problems become more apparent.

57.5.1 Intellectual Abilities

An apparently intact intellectual level frequently obscures other cognitive challenges and thus is not a reliable indicator of recovery following pediatric TBI. Nonetheless, studies using IQ as an outcome variable can yield some general findings as to overall patterns of recovery. A recent investigation by Crowe and colleagues⁵⁷ suggested that children sustaining a TBI in middle childhood actually had worse outcomes than did children sustaining injuries in early or late childhood. The investigators suggested that this result might reflect a window of vulnerability in brain maturation occurring during middle childhood. In another study, this group demonstrated significant decreases in intellectual functioning, assessed between the ages of 4 and 6 years, in children who sustained a severe TBI before the age of 3 years.⁵⁸ Ewing-Cobbs and collaborators⁵⁹ reported a similar finding when they observed continued deficits in intellectual functioning in children who had sustained a severe TBI before the age of 6 years and were followed for 5 years after injury. Conversely, Anderson and colleagues⁶⁰ showed that as a group, survivors of childhood TBI did not exhibit significant decreases in terms of intellectual abilities 10 years after injury, although these investigators cautioned that survivors of severe TBI had a less benign course. A recent study of adult survivors of pediatric TBI indicated relatively intact intellectual functioning, although significant decreases in IQ and quality of life were noted in those individuals who had sustained severe injuries.⁶¹ Head-injured children who have IQ scores within the normal range can, nonetheless, exhibit a variety of problems, some of them long term. For example, a study of children age 9 to 18 years injured approximately 4 years earlier demonstrated that IQ was not correlated with problem-solving skills within a social context.^{62,63} Another study noted that children with normal IQ scores exhibited subtle language differences in the classroom.⁶⁴

57.5.2 Motor and Visual-Motor Skills

Motor problems are perhaps the most easily recognized sequelae of head injury and are observed to some degree in nearly all children after moderate to severe head injury. Early work by Levin and Eisenberg identified deficits on tests of stereognosis, finger localization, and graphesthesia in approximately 25% of children with severe head injuries.⁶⁵ Others have shown that children with severe injuries are most affected when balance and speed of performance are essential to successful task completion. In a recent investigation, Sutton and colleagues⁶⁶ found that children with TBI exhibited significant decrements on a measure of visual-motor integration skills when compared with a population of children who had attention-deficit/hyperactivity disorder (ADHD). A series of investigations by Caeyenberghs and collaborators indicated not only that children with TBI exhibit a variety of motor impairments, including difficulties with manual dexterity, hand-eye coordination, and postural control, but also that many of these motor anomalies are associated with changes to white matter tracts (see Caeyenberghs et al⁶⁷⁻⁷⁰). Residual motor deficits have long-lasting functional significance in recreational activities and, later, in the workplace. A 1996 study⁷¹ described strength, agility, and coordination problems that limited children's participation in sports. Emanuelson et al⁷² described fine-motor deficits severe enough to affect

vocational outcome for as long as 7 years after severe injury during childhood or adolescence.

57.5.3 Speech and Language

Severe oral-motor disturbances, including dysarthria and dysphagia, are rare throughout the entire spectrum of pediatric TBI; however, Morgan et al indicated that these conditions are significantly more common following severe injury (upward of 75% of survivors of severe pediatric TBI) and can have profound effects upon recovery.⁷³ Spontaneous mutism and classic aphasic syndromes, including dyscalculia, dysgraphia, and expressive aphasia, are commonly observed in the acute recovery phase, although these effects are usually not long term.⁷⁴ On the other hand, researchers have shown that communication problems are often present in children who do not demonstrate aphasia and that these deficits can persist, particularly after severe head injury.⁷⁵ These linguistic impairments can include increased latency in naming objects, reduced verbal fluency, problems in writing to dictation, difficulty copying sentences, problems with written expression, particularly production speed and complexity, and slower-than-normal spontaneous speech.⁷⁴

Expressive and Receptive Language

Residual communication deficits after childhood head injury are common^{10,14,62} and can occur after head injury of any degree of severity. Research suggests that deficits noted after severe injury persist for years and substantially impact quality of life.^{10,15,16} A controlled study of youngsters aged 3 through 7 years at the time of head injury identified no differences between groups with respect to intellectual ability, adaptive competence, or behavior when the children were compared with healthy, appropriately matched peers. However, small but significant differences persisted for 2½ years after injury on a verbal test that required the comprehension and integration of complex material and on a verbal fluency task.¹⁷ Another longitudinal study of children injured between the ages of 5 and 15 years found that severe head injury adversely affected verbal fluency for as long as 5 years after injury. In comparison with children who had milder injury, their rate of language development was slower and did not reach the level predicted for their age. In addition, children injured at a younger age had a slower rate of recovery than did children who were injured when they were older.¹⁴ Hanten et al⁷⁶ found continued deficits in expressive language abilities during a 2-year follow-up of children with moderate to severe TBIs when they were compared with children who had sustained only mild injuries. However, participants within all three groups exhibited a similar trajectory of improvement. Results also indicated that younger children demonstrated more deficits regardless of injury severity and that children from higher socioeconomic levels demonstrated a faster rate of recovery of skills.

Long-term difficulties (i.e., 1 year or more after injury) have been observed in more foundational language tasks, such as confrontation naming and phonologic word retrieval.⁷⁷ Language disruption following pediatric TBI has also been demonstrated with functional brain imaging techniques. A 2007 investigation showed changes in activation patterns within

language-related cortical areas in a group of children who had sustained a closed head injury when they were compared with normal controls.¹⁸ Interestingly, these alterations were correlated with performance on neuropsychological measures of linguistic abilities, and changes occurred even though many of the participants with TBI exhibited relatively few structural lesions on conventional MR imaging.

Pragmatic Language

Impairment of pragmatic language may be observed in children after head injury.¹⁵ Pragmatic language, or discourse, is defined as language, either narrative or conversational, that is used to communicate with others and to meet the speaker's needs. Literature suggests the sparing of language capacity in young children who have undergone hemispherectomy, and the effect of head injury on developing linguistic skills is of particular interest.³⁵ Dennis and Barnes found that after severe head injury, children were most deficient in tasks that required understanding inference and intentions—abilities that have a significant impact on classroom performance.²⁰ Chapman and collaborators²¹ found deficits in discourse skills in children who had sustained either a mild or severe TBI when they were compared with uninjured peers. The investigators also demonstrated that working memory skills were correlated with discourse performance. Deficits in pragmatic language are also associated with social outcome, and these issues can become more salient as children mature.⁶³

57.5.4 Memory and Learning

Memory impairments are perhaps the most commonly discussed sequelae of brain injury in children. Deficits in *explicit memory*, which is the conscious recollection of previous experience (i.e., free recall, cued recall, and recognition), that occur after head injury in school-aged children are well characterized elsewhere.^{22,23,26,27,75,78} Anderson et al⁴⁸ are one of the few research groups to study the recovery of memory in young children, probably because the memory tests available for this age group are limited. Their research demonstrated that in the acute recovery period, younger children across the spectrum of injury severity exhibited memory problems. Although a more robust relationship between memory impairment and injury severity developed over time, there was also evidence that memory and learning actually *deteriorated* or failed to progress in some youngsters with moderate to severe injury. In a subsequent investigation, Anderson and Cattoppa⁷⁹ demonstrated that children with severe TBI injured during middle childhood exhibited long-term deficits in complex verbal memory abilities assessed at 5 years after injury. These authors also observed persistent deficits in verbal and visual memory skills in children sustaining a severe TBI and indicated that these deficits were associated with academic performance.⁸⁰ In a unique investigation, Salorio and colleagues⁸¹ reported that performance on a verbal learning task at 1 year after injury was strongly related to the volume of brain lesions outside the frontotemporal areas. The authors speculated that these results were indicative of diffuse axonal injuries that disrupted connections important for memory encoding, consolidation, and retrieval processes.

It is also important to consider how head injury affects prospective memory. In contrast to the recall of events from the past, *prospective memory* is the recall of intentions to be performed at a future time.⁸² Prospective memory is described as event-based (i.e., there is an external cue such as a timer), time-based (i.e., a scheduled appointment), or activity-based (i.e., a specific action is to be performed either before or after another event). Activity-based prospective memory is the only task that does not require the interruption of ongoing activities. As these examples illustrate, prospective memory supports adaptive behavior, such as completing errands, keeping appointments, or following instructions at a future time. Research shows that prospective memory develops early in life, being reported in children as young as 2 years. In one of the first studies in this area, researchers evaluated prospective memory in a sample of children 5 years after severe TBI.⁸² Performing a challenging mental task for less than 15 minutes resulted in prospective memory failures in more than 90% of the severely head-injured group. Furthermore, prospective memory deficiency remained even after a reminder had been provided. Difficulties in prospective memory were related to everyday problems, including maintaining the intention to complete a task in the face of ongoing attentional and task demands. Simple reminders or cues did not improve performance, suggesting that different strategies are needed to improve functioning. In a series of more recent investigations, McCauley and collaborators demonstrated that the prospective memory skills of children with TBI can be improved in tasks with a high incentive value (e.g., a large versus a small monetary reward).^{83–85} However, these investigators cautioned that although the group with severe TBI exhibited some improvements, their performance within the high-motivation condition continued to fall short of that of the control group under the low-motivation condition, suggesting persistent and significant deficits in prospective memory skills in children sustaining a severe TBI.⁸³

Recent investigations have also addressed *implicit memory* after childhood brain injury. Implicit memory occurs and can be demonstrated without deliberate awareness. Two examples include priming (i.e., the facilitation of learning that occurs by prior exposure to a stimulus) and procedural learning (e.g., skiing or maze learning). For a review of this literature, see Schacter et al.²⁰ Shum et al.⁸⁶ used a visual priming task to study implicit memory in a group of children aged 8 through 14 years with severe head injury and in healthy controls. The children were shown picture fragments and later the complete pictures intermixed with a group of novel pictures. Both groups showed an equal priming effect despite group differences on an explicit memory task. Noting the possibility of dissociation between various types of implicit memory, the investigators compared a group of moderately to severely head-injured children with a group of healthy controls on a measure of procedural memory.⁸⁷ No significant differences between groups were identified on either a rotary pursuit task or a mirror-reading task. However, in a recent investigation, Lah and colleagues⁸⁸ found that children sustaining a TBI before the age of 6 years exhibited deficits on measures of implicit as well as explicit memory when compared with either children injured later in childhood or uninjured controls. Given these mixed findings, future studies that evaluate different types of implicit memory skills following pediatric TBI occurring at various ages appear warranted.

57.5.5 Attention and Executive Function

Because trauma commonly affects the macrostructure and microstructure of frontal brain regions either directly or indirectly,⁸⁹ a marked trend in recent outcome research is to delineate more clearly the deficits associated with injury to these frontal brain regions. Frontal lobe injury, in particular, accounts for deficits in higher-order attentional skills, problem solving, planning, judgment, and information processing, as well as the personality changes frequently observed in children with TBI. These higher-level abilities, grouped under the rubric of executive function, serve to manage and coordinate both cognition and behavior.⁹⁰ The long-term impact of the disruption of executive skills that occurs during childhood remains poorly understood.⁹¹ However, the assessment of executive abilities in the near term after traumatic head injury provides the critical information necessary to plan subsequent interventions.

In a review of the extant literature on attention deficits following pediatric TBI, Ginstfeldt and Emanuelson⁹² suggested that divided attention and sustained attention appear most vulnerable to closed head injury, whereas simple attention span is more robust to disruption. These authors also indicate that most of the significant gains in attention skills can be expected within the first year after injury, with many individuals experiencing persistent deficits into adulthood. Interestingly, a study by Thaler and colleagues⁹³ observed differences between component aspects of attention skills in children following TBI and children diagnosed with ADHD. These authors indicated that children sustaining a TBI exhibited difficulties in the domains of focus and encoding, whereas children with primary ADHD exhibited difficulties in the domains of sustaining and encoding. These and other findings (see Anderson et al.,⁹⁴ Kramer et al.,⁹⁵ Levin et al.,⁹⁶ and Sinopoli et al.⁹⁷) suggest that children with attention problems secondary to TBI exhibit a neurocognitive and symptom profile that differentiates them from children with a diagnosis of idiopathic ADHD. In a 2011 investigation,⁹⁸ Catroppa and colleagues indicated that at 10 years after injury, attentional skills were not normally developed in a group of children who had sustained severe head injuries before the age of 6 years.⁹⁹ This investigation indicated that attention abilities developing early and more complex attentional skills developing later appeared most vulnerable to an injury sustained in the preschool period.

Working memory is an aspect of memory subsumed by the frontal brain regions that has recently received scrutiny in the pediatric outcome literature. Working memory is of limited capacity and is age-dependent. Through processes of storing, monitoring, and manipulating information, working memory mediates the development of many complex cognitive processes and academic skills.¹⁰⁰ Noting the vulnerability of the prefrontal regions to closed head injury and the structure of the frontal lobes, Levin et al.⁸⁹ investigated the impact of head injury on working memory in children. The investigators used a working memory test that allowed adjustment of the memory load (the n-back task) and evaluated children across the spectrum of injury severity at 3, 6, 12, and 24 months after injury. Children who sustained severe injury showed a decline in working memory between 1 and 2 years after injury, whereas less severely injured patients continued to demonstrate age-

appropriate gains. In a recent investigation, Gorman and colleagues¹⁰¹ demonstrated deficits in visual and verbal working memory skills following pediatric TBI. This study also indicated that these difficulties were not secondary to other executive dysfunctions (e.g., problems with inhibitory control).¹⁰²

Research is beginning to elaborate on the impact of metacognition on the executive abilities of children who have experienced severe head injury. According to information-processing theory,¹⁰³ metacognition refers to self-regulatory activities that monitor performance effectiveness and adjust strategies to enhance performance. With respect to memory ability, metacognitive management (i.e., employment of effective memory-enhancing strategies) usually begins to develop at the age of 6 years. Hanten et al¹⁰⁴ investigated metacognitive judgment in nine 7- to 13-year-old children, seven of whom had documented frontal injury. In this controlled study, children were asked to make two predictions: (1) how easy it would be to memorize each word in a 15-word list and (2) how many words from the list would be recalled after a 2-hour delay. Interestingly, the head-injured group showed no significant difference in learning when compared with the control group. In contrast, the head-injured group evidenced significant impairment in both predictions of task ease and performance level during the recall task. A study by Crowther et al¹⁰⁵ also demonstrated that children with moderate or severe TBI exhibited changes in their learning strategies and meta-memory judgments over a 2-year follow-up interval when compared with children who had sustained only a mild injury. Interestingly, although children with moderate or severe TBI demonstrated a faster rate of improvement in their performance during the first 12 months after injury, their scores peaked at this time point and then gradually began to diverge from those of children in the mild injury group between 12 and 24 months after injury.

A recent investigation by Wilson et al¹⁰⁶ indicated that adolescents who had sustained a TBI reported significantly fewer metacognitive, but not behavioral executive, deficits than their parents did. The number of their reports was also decreased when they were evaluated against the self-reports of uninjured age-matched peers. The authors suggest these findings are indicative of deficits in self-awareness and understanding of limitations within the TBI group. Taken together, these findings suggest that children who sustain a significant head injury can exhibit a general metacognitive deficit when asked to assess their own level of skill, the difficulty of a task, or the cognitive demands necessary for successful task completion. Finally, the pattern of results observed in the study of Crowther et al¹⁰⁷ suggests that children with moderate or severe injuries may make significant gains in meta-memory judgments in the first year after injury but may evidence a lag in age-appropriate maturational processes after this initial burst of recovery.

The impact of executive deficits is not limited to performance on working memory or meta-memory tasks. Aspects of social problem solving and behavioral regulation have been shown to be associated with the severity of injury to the frontal brain regions.^{108,109} Janusz and colleagues⁶⁴ investigated social problem-solving skills with a developmental model of social reasoning. The relationship between developmental level and social outcome was compared in three injury groups: severe head injury, mild head injury, and orthopedic injury. Findings indicated that children with severe head injury defined social dilemmas

and generated alternative solutions at the same developmental level as the control children. However, the *quality* of their solutions was poorer—that is, they described lower-level strategies as the “best” solution and used lower-level reasoning to evaluate the effectiveness of their strategies. In a similar investigation, Ganesalingam et al¹¹⁰ demonstrated that the social problem-solving difficulties of children with TBI were associated with deficits in self-regulation as assessed by performance measures and parent and teacher reports. A study by Levin et al¹¹¹ demonstrated that measures of cognitive control (e.g., working memory and inhibition) were positively related to social outcomes at 12 months after injury as assessed by the VABS. This study also showed that the relationship was stronger in children from lower socioeconomic backgrounds, suggesting an interaction between socioeconomic status and postinjury social outcomes.

Problem Behaviors

Behavioral changes within the 2-year recovery period are now well characterized in the outcome literature. Research in the 1980s and early 1990s established that premorbid psychiatric disturbances and severity of trauma were the best predictors of postinjury behavior problems. A significant number of children developed new behavior problems after head injury. Cole and colleagues¹¹² demonstrated that increases in aggressive behavior are very common following pediatric TBI. Furthermore, children with preexisting attention problems and anxiety as well as children with higher levels of disability were at the greatest risk for developing symptoms of aggression at 1 year after injury. A follow-up investigation by Gerring et al⁴² demonstrated that the prevalence of preinjury conduct disorder in children sustaining a TBI was higher than that in an age-matched and demographically matched population, but the TBI group also displayed a significantly higher rate of conduct disorder and disruptive behavior symptoms at 1 year after injury in comparison with uninjured, matched controls. A recent investigation by Max et al¹¹³ indicated that approximately 50% of children sustaining a moderate to severe head injury developed symptoms of a novel psychiatric diagnosis at 3 months after injury. This was compared with 13% of orthopedically injured controls and was not accounted for by preinjury functioning, family psychiatric history, or environmental factors.

Noting that behavior problems often persist well past the 2-year recovery period, recent work has attempted to characterize the behavior problems in children with head injury that fail to resolve^{63,64,114,115} or even worsen over time.^{108,109} A controlled study by Taylor et al⁶² investigated behavior over a 4-year period by comparing children who had moderate or severe head injury with an orthopedic control group. The level of behavior problems did not change as a function of time (i.e., short-term vs. long-term follow-up), suggesting the stability of these sequelae. Children in both the severe- and the moderate-injury groups showed poorer competence (i.e., school performance, activities, and social function) and everyday communication skills in comparison with the children who had orthopedic injuries. As the authors noted, a portion of children with moderate and severe injuries exhibited behavior problems for as long as 4 years after injury. These were exacerbated by family

environments characterized by limited resources and poor overall functioning.

Academic Skills

Numerous studies have documented changes in academic functioning following pediatric TBI. Taylor and colleagues¹¹⁶ examined school readiness skills in a group of children who had sustained a TBI before 6 years of age. Results indicated that children within the severe TBI group exhibited decrements in school readiness skills at a 6-month follow-up. Performance was predicted by injury-related variables and to some degree was moderated by environmental factors. A study by Ewing-Cobbs et al¹¹⁷ found that children who had sustained a TBI showed significant improvement in terms of academic skills performance over a 2-year follow-up interval; however, children in the severe TBI group continued to demonstrate marked deficits across academic domains. Children who were younger at the time of injury exhibited a decelerating rate of improvement in academic skills when compared with children who sustained similar injuries at an older age. In another investigation, Ewing-Cobbs et al¹¹⁸ demonstrated that children who had sustained a TBI before 6 years of age continued to exhibit academic deficits at a mean of 5 years after injury. This study also found that 50% of children in the TBI group had either failed an academic grade or required a primary placement in a special education classroom. Hanten and colleagues⁷⁶ demonstrated impairments in reading comprehension scores in children with severe TBI when compared with children sustaining either mild or moderate head injuries. Interestingly, this study indicated that lower-level reading skills, including reading rate, accuracy, and decoding skills, did not differ between children with mild, moderate, or severe TBI. Similar to the Ewing-Cobbs investigations, this study found that children injured at an earlier age experienced more difficulties in reading comprehension skills regardless of their age at the time of assessment.

Written language skills also appear to be affected by the severity of injury and age at injury. In one study of children and adolescents, written language was more impaired in the children in the sample who were between the ages of 5 to 10 years, an effect not seen in naming, expressive, and receptive language skills.¹¹⁹ Because written language skills show the most rapid development between the ages of 6 and 8, this finding lends support to the idea that developing abilities are those most vulnerable to disruption by brain injury.

57.6 Treatment and Rehabilitation

Although the acute outcome of children with head injury is necessarily of primary interest to the readers of this text, the treatment of the longer-term consequences of head injury is also relevant. Previously, we have discussed chronic difficulties with attention, organization, information processing, working memory, and problem solving that directly influence

learning. These cognitive deficits often lead to academic delays, significant behavioral disturbances, difficulties with socialization, family discord, and long-term problems with vocational attainment, all of which are appropriate targets for intervention.

57.6.1 Pharmacologic Treatment of Frontal Lobe Symptoms

Despite the vital influence that attention, monitoring, and organization have on learning, there continues to be a dearth of information regarding effective pharmacologic interventions directed at the specific cortical systems that subsume those cognitive functions and are perturbed by closed head injuries.¹²⁰ Amantadine hydrochloride (AMH), a dopamine agonist, has a long history of use in the pediatric population, although few empiric investigations have been conducted of its effectiveness in pediatric patients with TBI. Beers and colleagues completed a small pilot investigation examining the ability of AMH to improve outcome in pediatric patients following TBI.¹²¹ Children with a history of head injury who were experiencing clinically significant symptoms of executive dysfunction were randomized to treatment or to a usual and customary care condition. Neuropsychological assessment was completed at baseline and immediately after the 12-week treatment phase. Among the children who received AMH, the side effects were generally mild and remitted after the first week. Results indicated that children in the medication group evidenced statistically significant improvement in comparison with children in the usual care group in parent-reported measures of executive skills and promising trends in laboratory measures of executive abilities. These results are tempered by the lack of a placebo-controlled design. Small sample size also limits the ability to ascertain the important effects of age, gender, and injury level on response to AMH. A more recent pilot study by Scott et al¹²² indicated that ziprasidone may reduce symptoms of agitation and aggression in the acute stage of recovery after pediatric TBI. For a thorough review of the medication management options for pediatric patients with TBI, please see Pangilinan et al.¹²³

57.6.2 Cognitive Rehabilitation

As discussed throughout this chapter, impairments of cognition and behavior after traumatic head injury often persist long after neurologic symptoms have remitted.¹²⁴ Thus, although children with severe head injury usually receive inpatient rehabilitation services, longer-term services at home and sometimes at school are often needed. This rehabilitation is optimally completed by an interdisciplinary team of physical therapists, occupational therapists, speech pathologists, psychologists, educators, and parents, with the specific goal of the child's successful reintegration at home and in school.¹²⁵ Children with brain injury frequently benefit from secondary interventions that they complete with parents and the schools. Unfortunately, few empiric studies have assessed the efficacy of any of these interventions.

Rehabilitation Programs

Understanding a child's pattern of cognitive and behavioral strengths and weaknesses is a critical component of successful cognitive rehabilitation programs. With this information in hand, rehabilitation specialists use a variety of techniques, with the common goal of establishing new patterns of cognitive activity by reinforcing or re-establishing previous patterns of behavior, using compensatory cognitive mechanisms to replace impaired abilities, providing external compensatory mechanisms, such as personal orthoses or increased structure and support, and providing therapeutic interventions that enable individuals to come to terms with their limitations, thereby improving their overall quality of life.¹²⁴ For a review of the approaches to cognitive rehabilitation and behavioral management used in pediatric TBI interventions, see Catroppa and Anderson,¹²⁶ Semrud-Clikeman,¹²⁷ and Ylvisaker et al.^{128,129}

Acknowledging the lack of efficacy studies in the pediatric literature and the ever-present problem of maintenance and generalization with extant techniques, Ylvisaker and Feeney¹²⁵ and Park and Ingles¹³⁰ propose what they term "context-sensitive" rehabilitation. One goal for such intervention techniques is to prevent predicted behavioral deterioration and social skills deficits from occurring in the longer term after brain injury. This approach recognizes that the effects of pediatric TBI on foundational skills like attention and executive functioning will in turn have profound effects on other cognitive domains as well as on the implementation and eventual success of rehabilitation programs. Intervention techniques, chosen on an individualized basis, might include those that are impairment-oriented (e.g., empirically validated retraining exercises), activity-oriented (e.g., *compensatory* strategies that allow the individual to participate in an activity with a support that reduces the disability without changing the underlying cognitive impairment), and participation-oriented (e.g., environmental modifications encompassing both the concrete environment and the psychosocial environment).

Efficacy studies of these context-sensitive rehabilitation procedures are limited. Two studies are of particular interest because they involved children. Feeney and Ylvisaker¹³¹ evaluated a context-sensitive support-oriented behavioral and cognitive intervention to improve the behavioral self-regulation of two children who had experienced brain injury 1 to 2 years earlier. Both children had sustained severe frontal injuries, and upon return to the classroom they exhibited serious cognitive and behavioral problems. The rehabilitation intervention, which included behavioral supports, cognitive supports, and specific routines to support deficient executive skills, was highly individualized and completed in the classroom. After the initial intervention had been completed, a maintenance program was continued at school and completed at home. Both children achieved acceptable levels of behavioral control within approximately 1 month. Training was provided to ensure that environmental modification and successful instructional techniques continued over the next school year. These highly individualized and labor-intensive procedures resulted in positive results

not only at 1-year follow-up but also for as long as 9 years after the initial injury.

Other, less labor-intensive cognitive interventions have also demonstrated some effectiveness. In a small pilot study of a Web-based cognitive rehabilitation intervention, Wade and collaborators¹³² found evidence of improvements in self-reported executive abilities in a group of adolescents after TBI when they were compared with an education-only group that had similar characteristics.

Family Interventions

In accordance with the growing body of research noting that a child's recovery from head injury is correlated with family function, many hospitals and rehabilitation programs now offer support services for parents. These groups provide a venue in which parents can express feelings and resolve emotional problems within the family. Evidence suggests that parenting interventions can be very beneficial in improving family functioning and in promoting functional recovery in children following a TBI.¹³³ In a recent case study, Cohen and colleagues¹³⁴ demonstrated the effectiveness of parent-child interaction therapy in reducing externalizing behavior problems and improving parent adjustment in an 11-year-old boy who had sustained a TBI. Interestingly, this case study successfully employed a therapeutic approach typically used in much younger children, suggesting that a flexible approach can be employed in the design of intervention programs for children and families coping with a TBI.

Some pilot programs have also begun to use Web-based curricula to facilitate the delivery of family and cognitive interventions. Although the evidence base is small, these pilot programs have shown promise for improving parent coping and family functioning in general, and in effecting modest gains in cognitive skills in children with a TBI.¹³⁵⁻¹³⁷ For a review and a discussion of guidelines for family interventions following pediatric TBI, see Cole et al.¹³⁸

School-Based Interventions

Almost all children who survive a TBI return to the classroom.¹³⁹ Because children experiencing the longer-term sequelae are now understood to have an educational disability, modifications and specialized instructional techniques have come under increased scrutiny.¹⁴⁰ Interventions provided in the school setting can include assistive technologies,¹⁴¹ curricular and classroom modifications, and specialized "pull-out" services (i.e., individual physical, occupational, and speech and language therapies). The provision of these educational modifications and services is based on an individualized educational plan that identifies appropriate learning criteria, specific instructional procedures and modifications, and the learning environment that best meets the needs of the individual child. The most successful individualized educational plans provide for a comprehensive assessment of the

student's strengths and weaknesses as well as for staff education regarding TBI.¹⁴² Interestingly, educators are beginning to recognize the degree of developmental disruption caused by dysexecutive symptoms and emphasize the remediation of executive skills with programs that address learning strategies¹⁴³ and social skills.¹⁴⁴ (See Szekeres and Meserve¹⁴⁰ for an extended discussion of these techniques.)

57.7 Summary and Conclusion

Head injury is the most frequent cause of acquired brain injury in children, with an incidence of approximately 100 hospitalizations per 100,000 persons. In contrast to the excellent recovery reported in most children sustaining mild head injury, those with moderate to severe head injury show adverse effects in the development in cognitive, language, motor, adaptive, and psychosocial domains. Apart from the severity of injury, age less than 5 years and an adverse family environment are related to persistent sequelae of head injury. Within the cognitive domain, intellectual ability as measured by conventional standardized tests frequently shows a trend toward recovery after severe head injury and eventually approximates the normal range in most children. However, deficits in explicit memory and learning, attention, and executive functions, such as planning and self-regulation, frequently persist despite the apparent recovery of intellectual ability. Although language deficits can be pervasive during the initial phases of recovery from severe head injury, pragmatic skills, including the organization and processing of narrative discourse, are among the most persistent communication deficits. Residual problems with learning and explicit memory, which frequently persist despite initial improvement, contribute to reduced academic achievement in children following moderate to severe head injury. In contrast, retention of overlearned skills and implicit learning are relatively preserved. Executive functions as measured by laboratory tasks, such as planning, metacognitive measures, such as estimating one's learning and retention, and self-regulation of behavior in daily activities as rated by parents and teachers are frequently impaired for long intervals after moderate to severe head injury. Information processing speed tends to slow after moderate to severe head injury and detracts from performance in various domains. Similarly, slowing of motor speed is a frequent sequela of moderate to severe injury. Importantly, more recent studies have reported unexpected late declines in cognitive skills, such as working memory and attention. Adaptive functioning in relation to age expectation can also decline following severe head injury. The integration of cognitive skills with social processing, as in social problem-solving tasks, appears to be a useful approach to elucidating the sequelae of severe head injury and holds potential for the development of effective behavior intervention. To date, researchers have proposed such interventions to mitigate disability after head injury in children, but evidence for their efficacy is generally limited to case reports and group studies that lack randomized, placebo-controlled designs. However, initial studies of both pharmacologic and cognitive interventions have reported positive results that serve to encourage clinical trials.

Pearls

- The assessment of outcome depends on a careful consideration of preinjury risk factors. In children, brain injury occurs to a developing brain. Recovery is correlated with preinjury factors that continue to influence development after brain injury, as well as with injury- and family-related factors that can affect recovery in various areas of functioning. Children may recover to their preinjury level but fail to maintain the same rate of development that they had before the injury occurred.
- The emotional, behavioral, and cognitive deficits associated with pediatric brain injury often do not stabilize after the usual 2-year recovery period. It is not unusual to identify new deficits as a child matures. This may surprise parents, who expect further recovery as opposed to increased problems as the child matures.
- The functional significance of injury to the frontal brain regions has received increased scrutiny over the past decade. The impact that impairment of higher-order attentional skills, problem solving, planning, and judgment (i.e., the executive deficits) has on social, educational, and personality function is increasingly appreciated.
- A comprehensive neuropsychological evaluation completed at 1 year after injury can help track recovery. In addition, because of the changing pattern of deficits that can occur through childhood, follow-up evaluations at regular intervals serve to refine treatment planning and educational interventions.
- Although the new cognitive rehabilitation programs and educational interventions developed to address deficient executive abilities appear promising, efficacy studies are lacking.

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58 Cranioplasty

James Tait Goodrich

The use of cranioplasties in the pediatric population has undergone a number of significant changes during the last 25 years. A newer appreciation has developed of what materials can be implanted in a child and what materials cannot.

To put the subject in perspective, this chapter begins with a historical introduction that reviews the techniques introduced by surgeons over the last several hundred years. The types of cranioplasties currently in use are reviewed specifically as they apply to children and adolescents. The fact that childhood is a phase of continual growth, and infancy of rapid growth, means that a great deal of thought has to go into the repair of cranial defects in this unique surgical population. Cranioplasty entails distinctive considerations in each pre-adult phase of life—infancy, childhood, and adolescence—and these, too, are discussed. The various cranioplasty repair materials are reviewed, along with their unique ability or inability to repair a defect well. Complex scalp injuries are often associated with cranioplasty; therefore, techniques for their repair are also reviewed.

58.1 Early History of Cranioplasty

In reviewing the history of repairing holes in the head, one is continually amazed by what our surgical brethren have used as materials for cranioplasties. A phenomenal variety of materials have been used over the years to repair holes in the head. Although not a surgeon, Hippocrates provided evidence of considerable surgical expertise in his writings on skull injuries. In dealing with comminuted compound fractures of the skull, Hippocrates advocated the removal of free skull fragments. In place of the bone, lint dressing soaked with wine was placed—an interesting and very early technique for achieving wound asepsis. The wound edges were pulled together and secured with adhesive lint segments.^{1–3}

The first printed work to deal with injuries to the head, *Tractatus de Fractura Calvae sive Cranei* (“Treatise on Fractures of the Calvaria or Cranium”), was written by Berengario da Carpi (ca. 1460–1530) and published in 1518.⁴ Berengario offered several suggestions for dealing with fractured skulls, some of which would not be accepted today: “When large parts of the skull are removed, the wound should be sprinkled with shredded dry gourd (*frustulum cucurbitae siccae*), which promotes healing. Smaller defects are covered with ‘flesh’ [*carne*]—this is done to allow free drainage of the *sanies*; after that time, unguents may be applied.”⁴ In the same period (1517), a European surgeon, Hans von Gersdorff (1455–1529), described a cranioplasty made of a mixture of wine and wood oil and packed with wood wool; this was compressed until it became hard.⁵ However, Gersdorff appropriately noted that it should not be pressed hard against the dura because to do so would be “deadly” (► Fig. 58.1).

In South America, in what is now Peru, the Chimu and then later the Inca were skilled surgeons when it came to the management of head injuries. Recently excavated human skulls reveal some of the earliest uses of metal implants to repair skull defects. In museum collections are a number of skulls that were

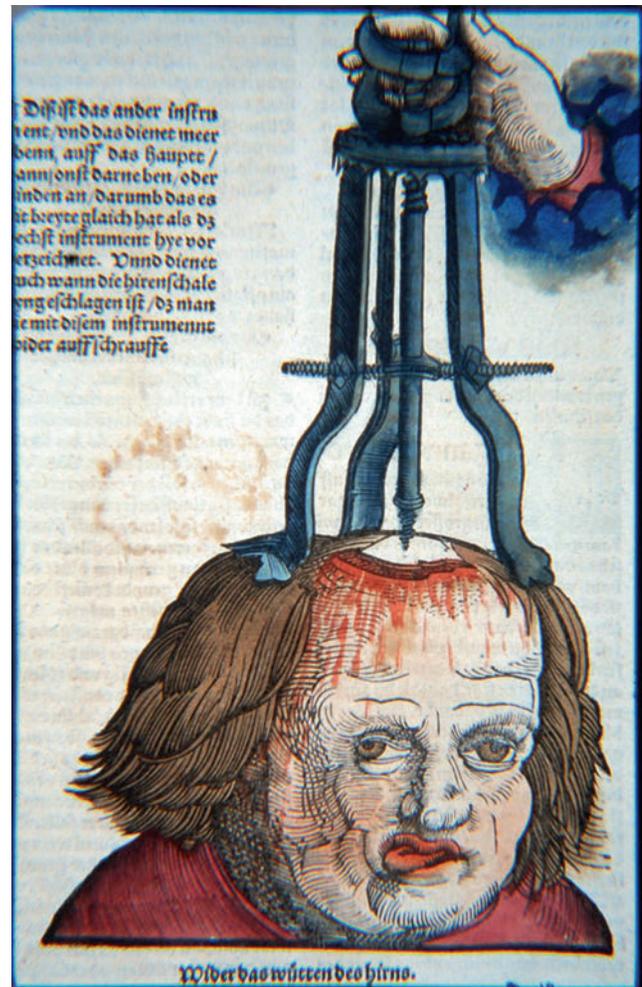


Fig. 58.1 Illustration from Gersdorff's classic surgical work⁵ in which he shows the technique of elevating a depressed skull fracture. He then forms a cranioplasty made from wood wool mixed with wine and wood oil to place back into the surgical defect. (Image courtesy of the University of Alabama Library, Reynolds Collection, Birmingham, Alabama.)

trephined, then repaired with gold or silver cranioplasties. These cranioplasties were well placed and contoured, and the patients clearly survived the surgeries with well-healed implants. Whether gold or silver was used appeared to be determined by the patient's social class. Metal plates of other types have also been advocated for use in repairing skull defects, as will be seen (► Fig. 58.2).

The concept of cleaning and replacing autologous bone in a craniotomy dates back to the brilliant French surgeon Ambroise Paré (1510–1590). Paré was performing autologous cranioplasties 500 years ago. His book *La Méthode Curative des Playes et Fractures de la Tete Humaine*⁶ contains an excellent description of the repair of skull fractures. Discussing the management of a large injury of this type, he noted that the bones were removed, and then he “turned them around and replaced them.” This technique of flipping over the bone flap is now in common use around the world. Paré also noted that he rarely covered cranial defects except those in the middle of the forehead, where for aesthetic reasons he used



Fig. 58.2 Early example of a successful cranioplasty (Peru, ca. 400 AD). The patient survived, as evidenced by the well-healed in situ cranioplasty made from a gold inlay. (Image courtesy of the Museum of Gold, Lima, Peru.)

plaster. For postoperative protection of the skull, Paré designed a molded leather helmet.^{6,7} One of the earliest illustrations of a “metal plate” cranioplasty appears in a book by Bellosté, *The Hospital Surgeon*.^{8,9} In both the French and English editions, published in the early 18th century, a frontispiece shows a surgeon placing a lead plate cranioplasty. In the text, Bellosté describes the procedure: “[W]hen the dura mater is uncov’r’d I prepare a plate of lead very thin, and very smooth, pierc’d it holes in several places with an inequality, cut and fitted to the bigness of the opening.” Interestingly, Bellosté observed that some patients reported discomfort around the cranioplasty site when the weather turned to extremes of hot or cold—“symptoms of the trephined”—a complaint still echoed today by patients in whom artificial and especially metal cranioplasty materials are used (► Fig. 58.3).

The use of skull bone material from nonhumans for cranioplasty dates back to at least the middle of the 17th century. In 1682, Job Janszoon van Meekerren (1611–1666) reported the case of a Russian soldier who had sustained a skull defect as a result of a war injury.¹⁰ An imaginative surgeon, he performed a cranioplasty with a piece of dog calvaria. Subsequently, the Catholic Church learned of this treatment, found it in violation of canon law, and ordered the dog bone to be removed. If the bone was not removed, the patient would be excommunicated. Unfortunately, we have no long-term follow-up of this case (► Fig. 58.4).

John Woodall (1570–1643) was an early advocate of the use of cleaned and debrided bone to close a cranioplasty defect. In



Fig. 58.3 Frontispiece engraving from Bellosté’s *The Hospital Surgeon* showing an 18th century surgeon performing a “lead plate” cranioplasty for a skull defect.⁸

The Surgeon’s Mate, published in London in 1617, Woodall stated that cleaned, fractured bone could be replaced without difficulty.¹¹ Woodall commented, nearly 400 years before the advent of high-speed pneumatic motors, that young surgeons who wished to trephine should practice first on the skulls of calves before attempting the procedure on a human skull—a remarkable early insight (► Fig. 58.5).

Over the years, a long list of foreign materials have been used to repair skull defects. In 1874, Ella reported a case of head injury in the South Seas in which the natives used coconut shells to repair the cranial defect.¹² ► Table 58.1 lists some of the materials used to repair defects over the course of the last two centuries.

58.2 Techniques of Cranioplasty

A cranioplasty is a procedure for repairing a defect of the calvaria. It can be accomplished in various ways. A successful cranioplasty is one in which the cranial defect is repaired and then heals and grows with the child in the anatomically and aesthetically most appropriate fashion. In the young infant (younger than 1 year), one can leave a cranial defect of up to 2 cm



Fig. 58.4 An unusual 17th century case reported by Meekeren on the use of a dog skull bone cranioplasty to repair a skull defect in a Russian soldier.¹⁰

open; as long as the dura and pericranium are intact, bone will commonly fill the defect. In older children, spontaneous repair becomes less likely, and substitutes and replacements for the missing bone must be considered.

In the management of craniofacial defects, the location is important. Defects in the frontoglabellar region require much more attention to detail than a defect behind the hairline. Contours, healing scars, alignment of eyebrows, and orbital dystopia all are important factors to be considered. Cranial defects can result from trauma, be congenitally acquired, or arise from infectious processes. Each of these etiologies has distinctive implications in both the timing and type of cranioplasty repair.

58.2.1 Preparation of the Cranial Defect

The preparation of a cranial defect remains the same in all cases, no matter what the source of the defect. The surgical bed must be clean and free of debris of any kind. Both the surgical bed and the overlying surgical flap must be well vascularized. Without these conditions, neither the flap nor the implant will heal. Preoperative planning has to take account of the nature and course of the scar, particularly so in cases of previous trauma. In many cases, it is best to incorporate the previous scar

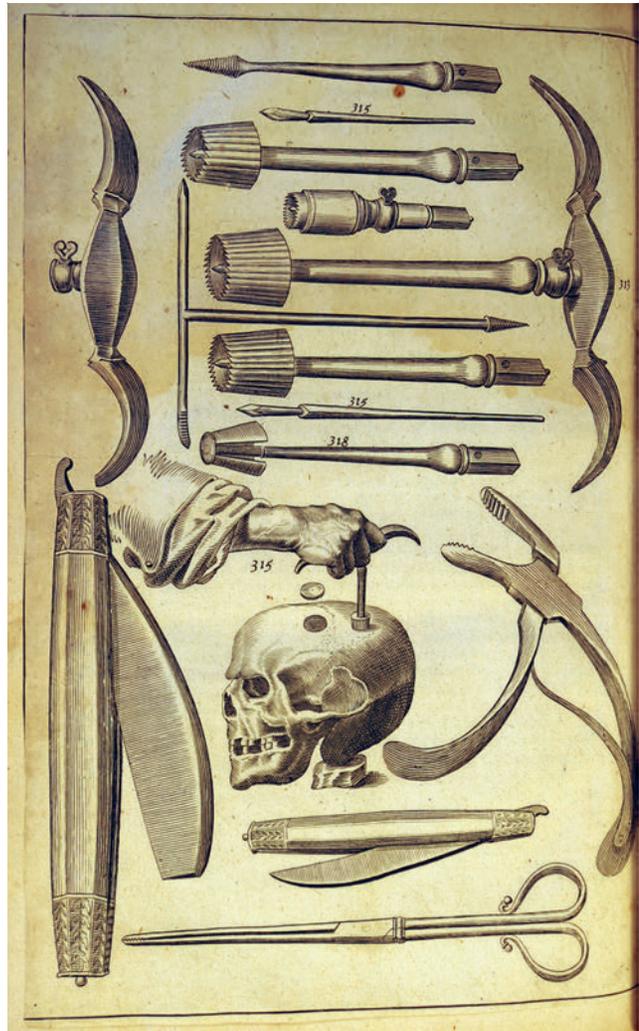


Fig. 58.5 Early surgical engraving from Woodall's *The Surgeon's Mate* showing typical surgical instruments used for trephination and the repair of skull defects in the 17th century.¹¹

Table 58.1 Materials used to repair skull defects during the course of the last two centuries

Author	Year	Material
Jaksch	1889	Eagle bone
Grekoff	1895	Calf scapula
Henschen	1916	Buffalo horn
Rehn	1912	Ox horn
Seydel	1889	Tibia
Keen	1905	Harvested bone chips from nearby skull
Kappis	1915	Rib grafts (first use)
Brown	1917	In situ split rib grafts (first use)
Mauclair	1914	Iliac crest bone
Roepke	1912	Bone from the scapula

Source: Adapted from Reeves DL. Cranioplasty. Springfield, IL: Charles C Thomas; 1950.

into the repair. Because parallel scars can disrupt blood supply and cause a flap to slough off, parallel incisions should mostly be avoided. If possible, it is best to keep surgical incisions and scars in hair-bearing areas.

In the case of craniofacial reconstructions in the vicinity of the frontal sinuses, it is extremely important to cranialize the sinus and in some cases to obliterate it with a pericranium flap. The frontal sinus does not typically become developed until the age of 3 to 4 years. When the skin flap is elevated, the pericranium is brought up as a second layer, with its vascular pedicle kept intact. This vascularized pedicle flap can be easily rotated into a number of different positions to cover defects and the frontal sinus. Bone edges that are to be incorporated in the repair have to be “freshened up”—that is, cleaned and debrided of any scar tissue or debris. The edges of the cranioplasty should be lightly burred with good irrigation to provide a fresh vascularized edge. We have switched to the use of “resorbable” bone wax for bone edge bleeding. In our experience, the older formulas of bone wax inhibited solid bony unions by blocking good osseous integration. Meticulous hemostasis and the gentle handling of soft tissues are always obligatory.¹³⁻¹⁶

58.2.2 Use of Autologous Bone in Cranioplastic Reconstructions

Autologous bone is always considered first as the primary repair material in cranial defects. Autologous bone heals best, will grow with the child, and has the lowest incidence of infection and extrusion.

Essentially four types of autologous bone are available to the neurosurgeon for reconstruction: (1) split calvarial bone grafts, (2) costochondral rib grafts, (3) iliac crest, and (4) fibula grafts.

In the management of open depressed skull fractures, it appears to be common practice around the world to discard the traumatized bone flap and at a later date repair the craniotomy defect with some form of artificial implant.¹⁶⁻²² For the last 27 years, the author has routinely removed the traumatized bone, cleaned and debrided it, and then placed it back (see below for technique). This technique has virtually eliminated the need for a secondary artificial cranioplasty, particularly in infants and children. Avoiding the placement of foreign material, such as methyl methacrylate, clearly reduces the rate of infection; in addition, we have found that such repairs deteriorate with time, and in infants and children, the skull can outgrow the plate, necessitating still more surgery.²³⁻²⁷ Other late-term complications include flap migration and sinkage plus painful symptoms associated with barometric and temperature changes, also referred to as the “syndrome of the trephined.”²⁸

The neurosurgical practice of discarding the “contaminated” bone is actually a relatively recent practice introduced around the time of the First World War. The practice was fairly well entrenched by the time of the Second World War. A review of general neurosurgical textbooks shows that the practice is widespread and considered routine by general neurosurgeons. More recently, it has become a more standard practice among pediatric neurosurgeons to remove, clean, and replace the autologous bone flap and thereby avoid a later artificial cranioplasty.^{29,30}

Replacing Autologous Bone: Surgical Technique

The original scar (if present, as in an open depressed fracture) is used to expose the traumatized bone. A standard craniotomy is then performed with a high-speed pneumatic or electric drill (e.g., Midas Rex; Medtronic, Minneapolis, MN) and a “footed” attachment (e.g., B-5R). The bone flap is removed in a “cookie” fashion, with a 2- to 3-mm bone margin added to the outer edge. The surgical wound is cleaned, debrided, and vigorously irrigated to remove any debris and foreign material. The flap is then soaked in a 10% povidone-iodine (Betadine) and saline solution for 15 minutes, and then the Betadine is allowed to dry. Before the bone flap is repositioned, it is again washed and soaked in physiologic saline solution to remove any excess Betadine solution. The use of undiluted Betadine is actually toxic to bone and is not recommended. The bone is never autoclaved, frozen, or irradiated because these techniques denature the bone protein matrix and provide an extremely poor biological matrix for repair. In those rare cases in which the bone flap is accidentally dropped on the operating room floor, this same technique has been used with no deleterious effects. To reiterate, bone wax (we now use only a bioresorbable wax) is used sparingly to stop bleeding. Many years of personal experience with craniofacial operations has revealed that bone wax, when placed into the diploë space, retards natural bone growth and osseous integration and can also act as a potential nidus of future infection. Our preferred technique is to place sterile sponges (Gelfoam; Pfizer, New York, NY) soaked in thrombin (or sometimes Avitene; Bristol Healthcare, New Delhi, India) against the bleeding bone with pressure. This material is removed once hemostasis has been obtained. To further enhance bone healing, we stabilize the bone flap with resorbable miniplates. We routinely administer antibiotics to these patients for a 48-hour period postoperatively; the antibiotics used are suited for skin organism coverage (e.g., oxacillin or nafcillin).

The rigid fixation of bone flaps is critical in the pediatric population. In the late 1980s, the use of metallic fixation plates became the technique of choice. Unfortunately, over time, we have learned of potential problems, with plates migrating and fixation screws backing out, among other issues. In children whose intracranial pressure may be increased (e.g., those with a craniofacial syndrome, such as Crouzon syndrome), the use of metallic plates is not the best choice. At later reoperations in several children, we found that the metallic plates had migrated intracranially, and some were actually within the dura or brain parenchyma.³¹⁻³⁴ Similar problems have resulted from the use of wire in young children. As a result of these issues, our surgical team now uses only bioresorbable plates and sutures (e.g., Vicryl or Nurolon; Ethicon, Somerville, NJ) to stabilize the flaps. These plates are typically resorbed by hydrolysis over a period of 8 months to 1 year. Because of their higher profile, the family should be made aware of them; parents notice them right away, typically when first bathing their child. We have also had several cases in which sterile granulomas have developed over the plates. The granulomas are almost always sterile, and to date we have had no infections, nor have any required surgical intervention. The plate granulomas typically resolved over 2 to 3 months. If a granuloma is red and tender, then infection has to be considered, but in our experience to date we have not encountered an infected plate.³¹⁻³⁴

Split-Thickness Calvarial Bone Grafts

In the growing child, the use of native materials for craniofacial and traumatic repairs remains the gold standard. The human skull, with its natural contours, provides the best source of bone for repairs.³⁵⁻³⁷ The skull has a natural mirror image that allows the surgeon to harvest calvarial bone, bone that often possesses a contour that closely matches the defect. In most children, by the age of 3 years the skull has become bilamellar and can be split along the diploë to obtain two pieces of bone, one placed in the defect and the other in the donor site. With a soft, malleable piece of metal, a template of the defect is designed and applied to the contralateral skull in various positions until an area is located that closely matches the defect to be repaired. The donor graft is always made 3 to 4 mm larger than the defect. This allows for the bite of the craniotomy drill and gives additional trimming room for positioning the donor graft. The flap is elevated with standard craniotomy techniques and copious irrigation so that the heat generated by the craniotome does

not burn the bone. As discussed above, the use of wax, other than resorbable wax on bleeding bone edges, is discouraged (► Fig. 58.6 and ► Fig. 58.7).

Once the bone flap has been elevated, there are a number of surgical techniques available for splitting the bone. In the very young child (younger than 2 years), a razor-sharp osteotome is used; it is handled much like a knife to “slice” the bone apart. We keep a special set of osteotomes that are used only for these procedures. The edges are routinely sharpened, and there can be no nicks or dings on the cutting edges. The osteotome set has to contain a number of different sizes and curves to be effective. Another option is the use of a No. 15 scalpel blade, again to “slice” the bone. The bone is held in the nondominant hand while cradled in a surgical towel. This is done to protect the hand in case the osteotome or scalpel should slip. The diploë does not develop until about 3 years of age, but there is usually some marrow space available, even in very young children. In older children, usually after the age of 3 to 4 years, the bone is thick

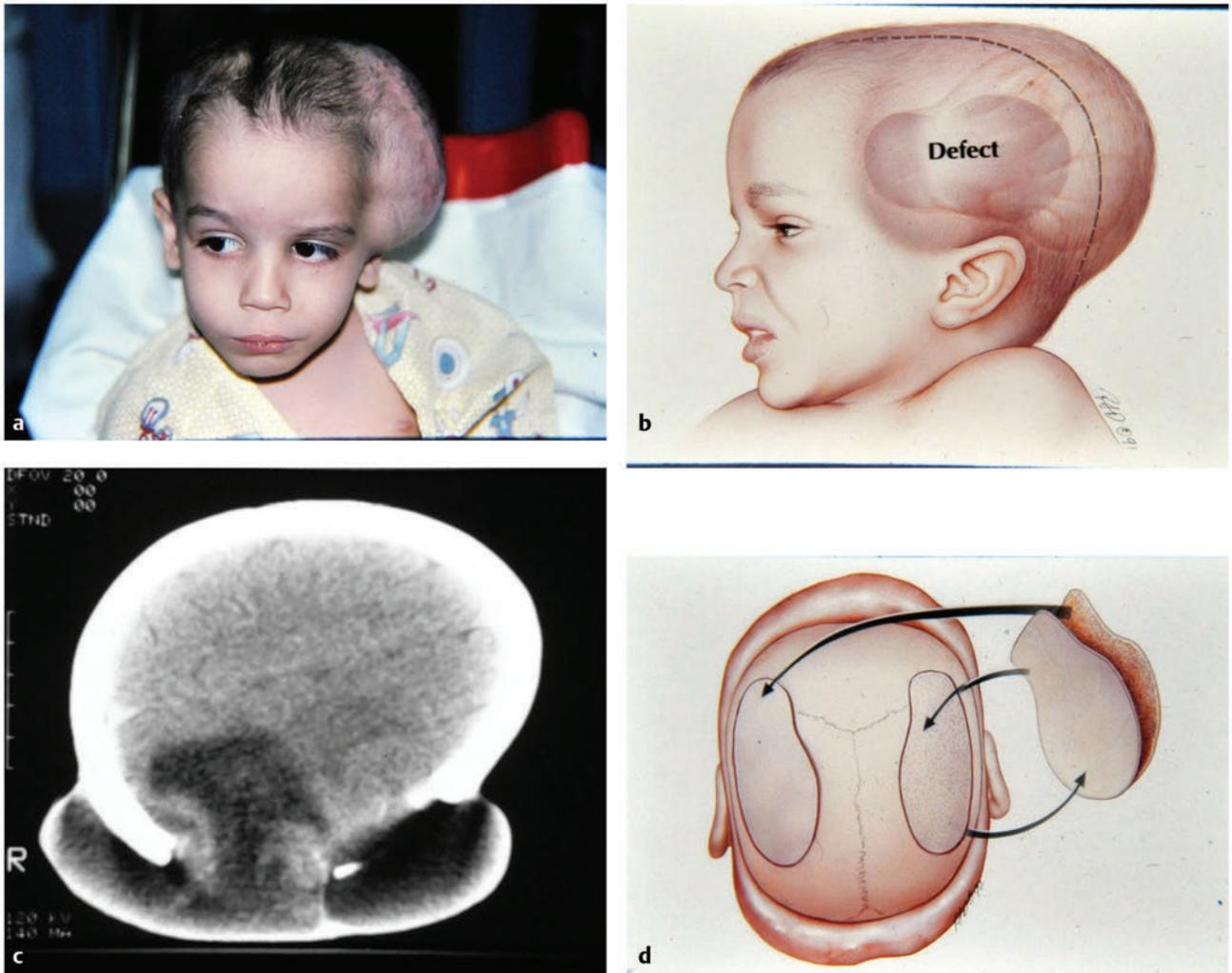


Fig. 58.6 (a) A 2-year-old boy who fell five stories and sustained a large parietal skull defect with a pseudomeningocele over the left parietotemporal region. (b) Artist's representation of the defect in the left lateral parietotemporal bone. An ideal case for harvesting a “mirror image.” (c) Axial computed tomographic (CT) scan showing the large skull defect and resultant pseudomeningocele, which will be repaired with a split-thickness calvarial bone graft from the opposite side. (d) Schematic showing the split technique, with harvesting of a “mirror image” piece of bone from the opposite side. The flap is elevated and split along the inner table, and the inner table goes to the graft site while the outer table goes to the defect site. (continued)

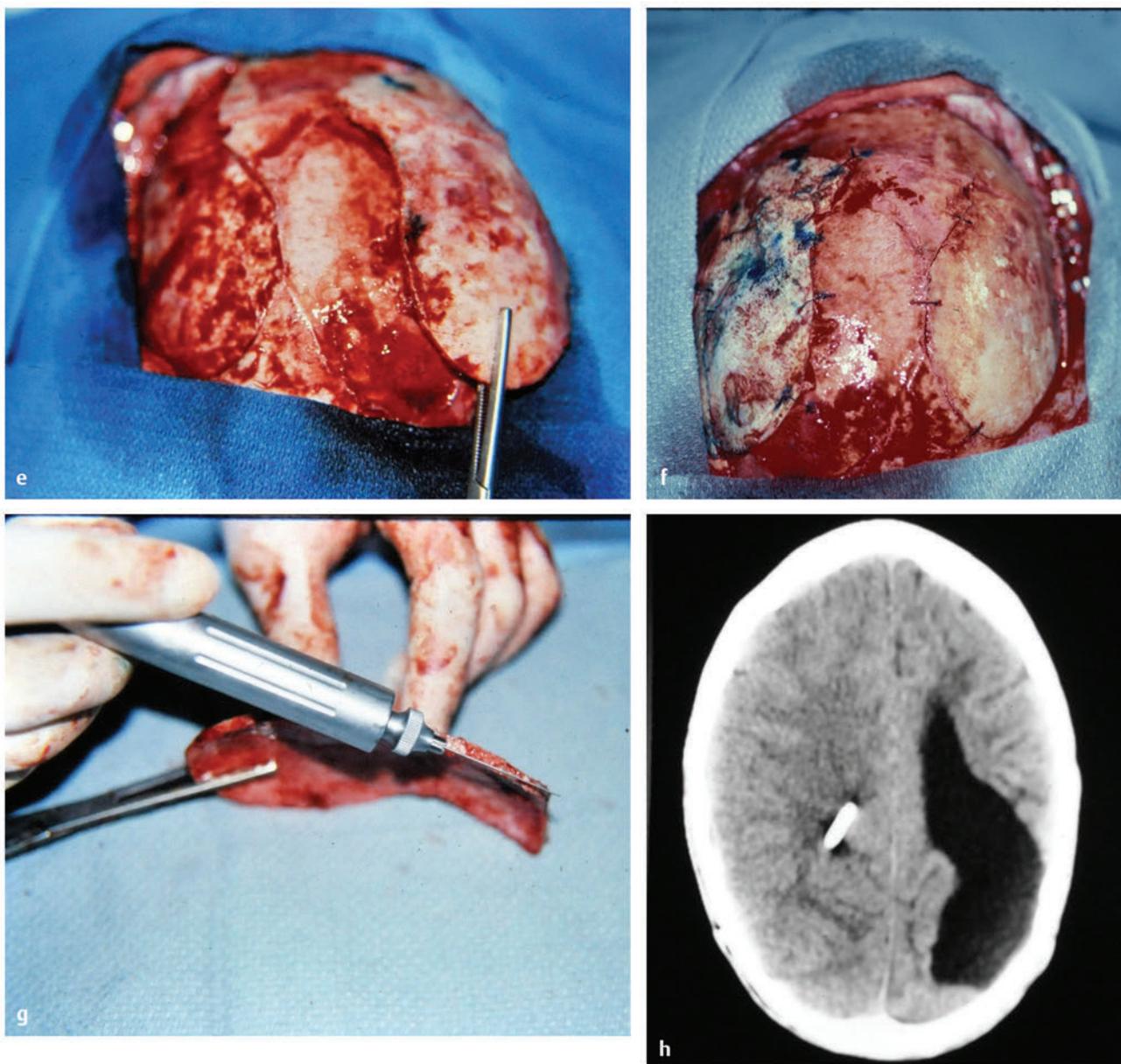


Fig. 58.6 (continued) (e) The full-thickness bone flap from the donor site (right parietotemporal region) is being elevated here and held by the Kelly clamp. (f) Both units of bone have been placed into position and anchored. The inner table has gone to the donor site on the right and the outer table to the defect site on the left. (g) A technique to split a full-thickness bone graft by using an oscillating saw and following the bone marrow space in the bone, just between the inner and outer tables of the skull bone. (h) CT of the patient done 8 years after the calvarial reconstruction with the split grafts shows the grafts now well incorporated. Additionally, no problems developed with displacement or infection in either bone graft. This patient has now been followed for more than 20 years, and there have been no further issues with the grafts.

enough to be split with fine, thin, high-speed tools such as the C-1 attachment for the Midas Rex. The splitting technique involves drilling a series of holes into the diploë space and then, in a side-to-side action, connecting the drilled holes. Depending on the diameter of the flap, curved osteotomes and reciprocating saws with flexible blades can also be helpful in splitting the bone. With some of the newer and thinner reciprocating/oscillating saw blades, we are now able to split bone in infants younger than 1 year of age. In the flap is very large, one can also cut the flap into two or four pieces, complete the splits, and then plate the units back together with miniplates (► Fig. 58.8 and ► Fig. 58.9).

The thickest bone for harvesting is over the frontal and parietal boss regions, and the thinnest is over the temporal regions—considerations to be kept in mind when bone is harvested. It is always desirable to create large bicoronal flap exposures when the need for large grafts is expected. In those cases in which additional bone contouring is necessary, we use what is called a “wagon wheel” technique. A full-thickness skull bone is elevated with the pericranium left on. The flap is then split, with the inner table going to the donor site. The outer table, with the pericranium kept moist and intact, is then contoured with a series of cuts that look like a “wagon wheel.” A circle cut is

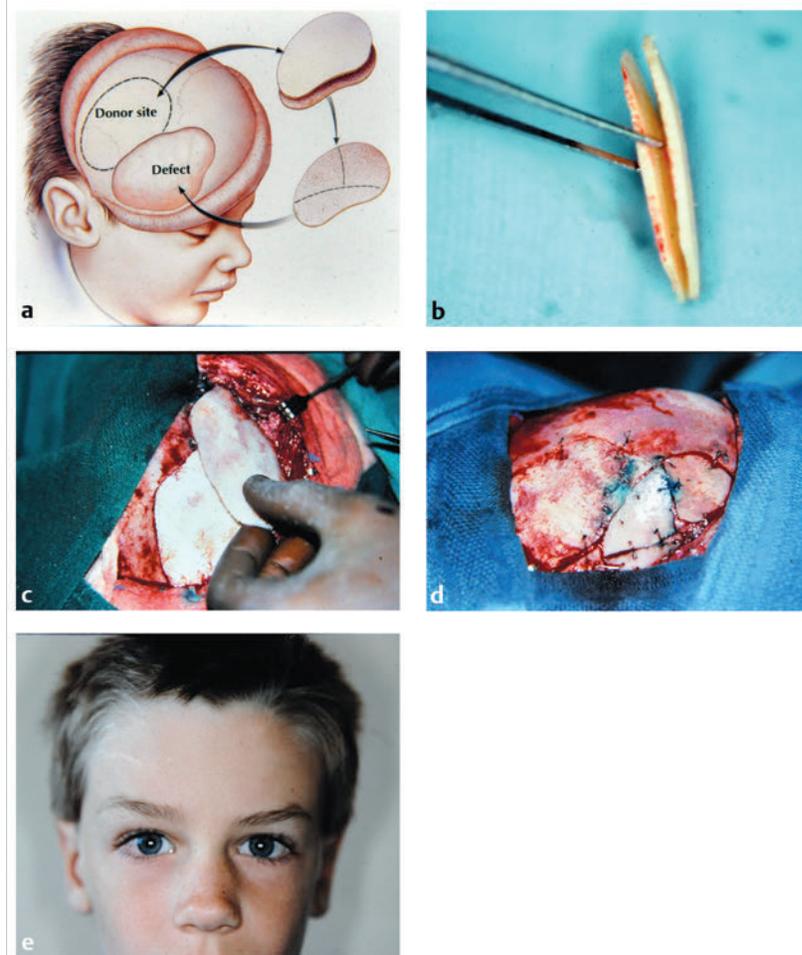


Fig. 58.7 (a) A 5-year-old boy who sustained a right fronto-orbital depressed skull fracture in a motor vehicle accident. He presented 2 years after the accident with a large right frontal skull defect. (b) After the bone flap is harvested, it is given to the plastic surgeon to create a split-thickness graft forming the two units of bone seen here. In this case, an oscillating saw was used with a “soft” flexible blade within the bone marrow. (c) The skull defect is exposed and debrided along the bone edges. Behind the defect, a craniotomy is marked matching the defect site. This unit of bone is elevated and split along the diploic space. One piece goes back to the donor site, and the other is cut and contoured to fill in the defect site. In this image, the donor site has been replaced, and the surgeon is marking out the cuts for the reconstruct of the forehead contours. (d) A view of the right side of the forehead showing the donor unit replaced posteriorly. Anteriorly, each of the bone units has been cut, contoured, and placed into position within the defect site. (e) The patient 3 years after surgery, during which time he maintained a symmetric forehead along with excellent orbital control. With now a 22-year follow-up, no relapse or loss of bone and no infection issues have occurred.

made in the middle, and a series of “spokes” are made from the circle to the edge of the flap. The pericranium is not cut, and the bone cuts are made down to the thickness of an eggshell. With gentle finger pressure, the bone can be fractured to the desired shape (► Fig. 58.10). This technique is particularly useful for desired bone contours in the orbits (roof and floor) and around the orbital rim (► Fig. 58.10).

Another technique for obtaining bone is the *in situ* outer-table craniotomy; it can be used in the older child and adolescent whose skull thickness is greater than 1 cm. The technique involves drilling a trough around the edges of the pre-designed bone template. The trough is carried into the diploë but not through the inner table. With the use of very sharp curved and straight osteotomes placed within the diploë, the outer table of bone is lifted off, with the inner table left intact to serve as the repair material. A reciprocating/oscillating saw can also be helpful once the plane has been developed with the application of osteotomes. In another technique, a Gigli saw is placed in the diploë, and by following the diploë, one can elevate the outer table. This technique has been particularly popular with plastic surgeons. It is necessary, however, to keep in mind the risk that the osteotome and/or saw blade can plunge through the patient’s thin bone into the brain, so extreme caution needs to be exercised when these techniques are used (► Fig. 58.12). The use of split-thickness grafts has many advantages and remains the standard for



Fig. 58.8 A split graft between the two tables of bone is made with a fine cutting tip (Midas Rex C-1 or X-1) placed into the bone marrow with a series of full penetrations. These “plunges” are then connected in a side-to-side motion. Copious irrigation is supplied to keep the bone from being burnt.

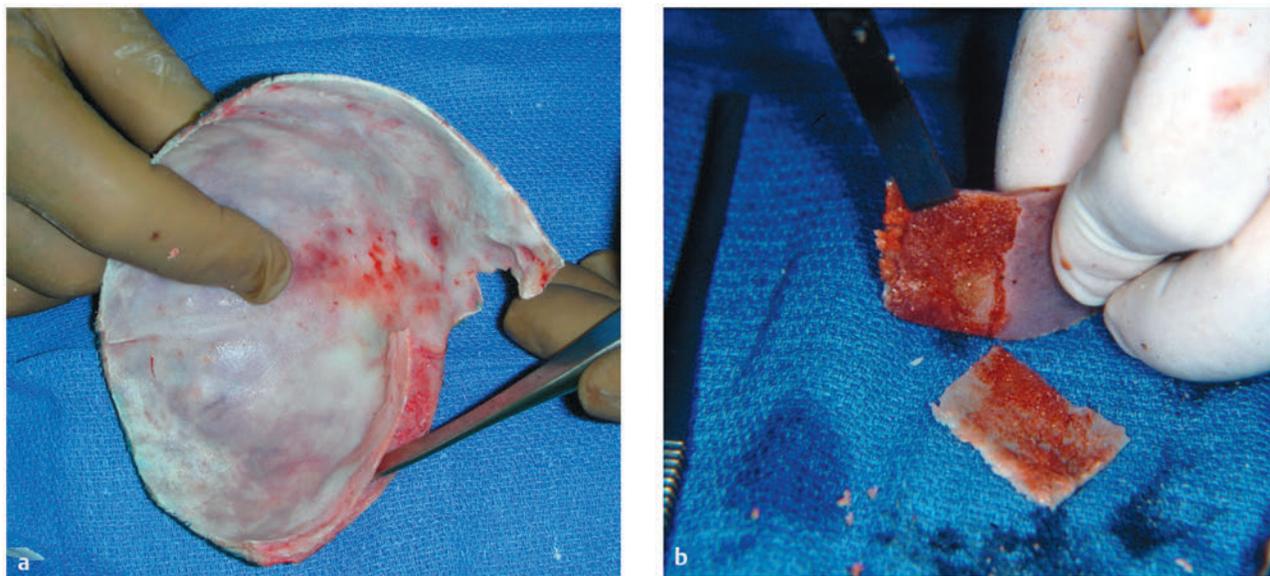


Fig. 58.9 (a) Technique of using a sharp osteotome like a “knife” and splitting along the marrow space. This is being done in a 6-month-old child with plagiocephaly for extra graft material. (b) In a very young child, the bone can be easily split with a fine sharp osteotome or a No. 15 scalpel blade. The instrument is used like a knife to split bone in the marrow space.

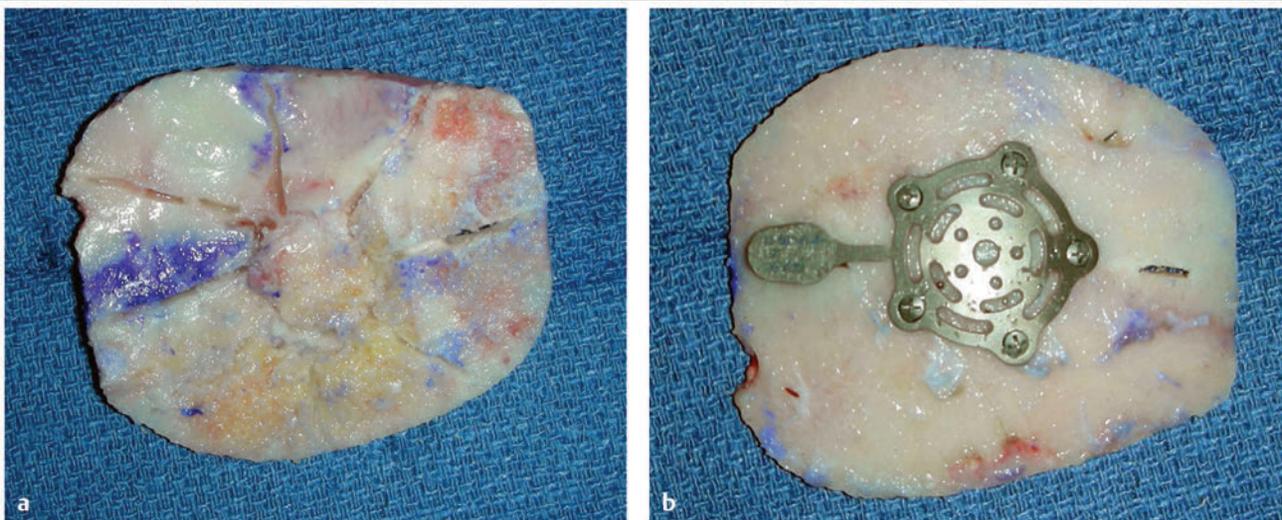


Fig. 58.10 (a) The “wagon wheel” technique for contouring bone. The bone is first split along the diploë, as described above. The pericranium has been left on the outer table. On the side opposite the pericranium, the “wagon wheel” cuts are made—a center circular cut and then a series of radiating cuts deep to the pericranium. The cuts are just made to the edge (i.e., an egg shell thickness). The pericranium holds the bone together, and with just gentle finger pressure the bone can be shaped in the desired contour. (b) With a fine bur or cutting tool, the radial cuts are made on the side opposite to the pericranium. The cuts are made in such a fashion that an “egg shell” thickness is left at the end of the cutting.

craniofacial repairs. The infection rate is very low in these cases. The risk for rejection is virtually nonexistent. The natural bony union that results grows with the child, an important consideration in younger patients.

Rib Grafts

Rib grafts have long been popular with plastic surgeons and have been used in various types of cranioplasties.^{38–40}

Furthermore, these grafts are a source of ample material that can be obtained easily and with low risk to the patient. An advantage of ribs is that they can be obtained from the patient in any of a number of surgical positions. On the anterior chest, the fourth through the sixth ribs are accessible; on the posterior chest, the eighth through the tenth ribs are accessible below the scapula; and in the lateral position with the patient’s arm abducted, the fourth through the eighth ribs are easily accessible.



Fig. 58.11 (a) The “spiral” technique for contouring bone. A full-thickness piece of calvarial bone of the desired size is harvested from the opposite side. As illustrated here, it is harvested from the right side, with the template designed on the left. (b) A full-thickness bone graft that has been elevated and split shows both the inner and outer tables. The inner-table graft on the right will be placed back in the donor site. The outer-table graft on the left will be contoured with a “spiral” technique. (c) The outer-table bone graft has been cut with a high-speed drill starting at the outer edge and then carried in a circular fashion to the center. With just gentle finger pressure, this split bone graft can be contoured to fit just about any area with a contour, such as the forehead or orbital roof and floor.

The graft site is exposed and prepared in standard fashion with fresh bone margins. The area is measured and the graft size determined. The rib grafts are harvested by making a skin incision directly over the ribs selected. This incision is carried down to the rib periosteum with a monopolar cautery and a fine needle tip on a low-current setting. The periosteum is separated from each rib with a Key-type periosteal elevator. As the rib is elevated, the neurovascular bundle and underlying periosteum and pleura are left intact and gently stripped away with a pigtail rib separator. In determining the rib length that is to be removed, be sure to allow *an additional 5 to 8 mm for the bending and contouring*. Each end of each rib is cut, removed from the field, and split longitudinally with a sharp osteotome, yielding two pieces that can now be bent and contoured with a Tessier rib bender. Because ribs are malleable and fracture easily, the splitting must be done slowly and carefully. Rather than apply a mallet to the osteotome, it is better to use the os-

teotome like a knife blade and slowly work your way through the rib in a “knifelike” fashion. The ribs are then positioned at the recipient site and shaped to fit the size and contour of the defect. It is desirable to create a graft whose height and contour are slightly exaggerated because there is typically some collapse and resorption of the graft over time.

Because rib is the most malleable of the materials available, it is particularly applicable to reconstruction around the orbits and over the forehead. In very large cranial defects, the “wire link fence” technique of Munro and Guyuron³⁹ can be useful. With a series of split ribs, the bone is woven together in a wire link fashion and then positioned as a craniotomy flap. The only problem with this technique is that over time the ribs can take on a “washboard” appearance, which is quite undesirable as far as aesthetics are concerned.

Some “pearls” to keep in mind in harvesting ribs and using them in reconstruction follow:

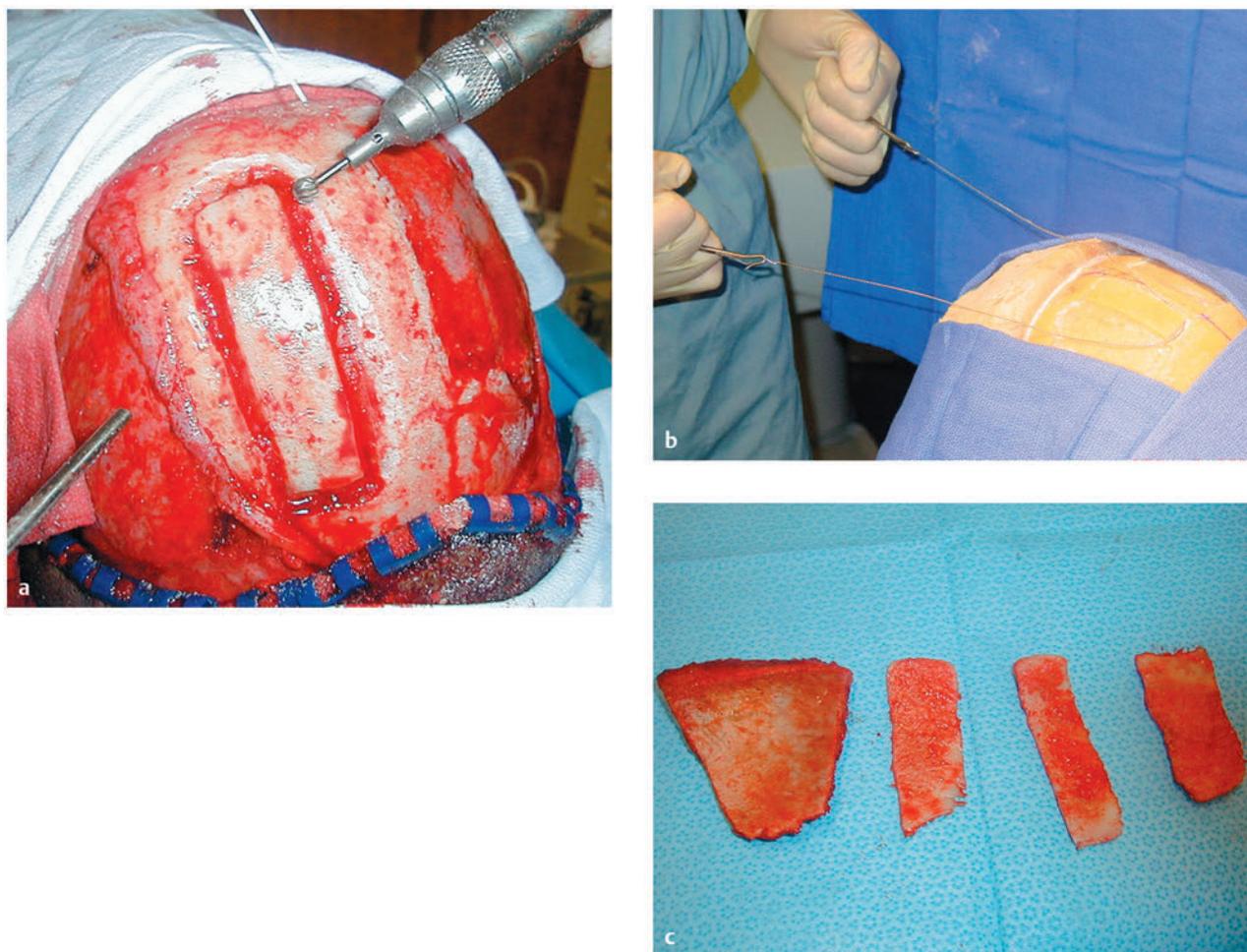


Fig. 58.12 (a) Technique for harvesting an outer-table bone graft. A trough is made in the skull bone to the level of the diploë with a round bur. (b) A Gigli saw is placed within the diploë, and the surgeon “travels” the saw within the diploë space. This technique requires some skill in using a Gigli saw, but it can successfully produce large pieces of graft bone of different contours and shapes. (c) Four split grafts obtained from a single patient by outer-table harvesting with the Gigli saw technique.

Pearls

- Never take more than two adjacent ribs; otherwise, a “flail” chest may develop.
- Always attempt to keep the rib periosteum intact because this will allow a rudimentary rib to form in the donor site.
- Should the pleura be violated and a pneumothorax occur, place a 10F red rubber catheter over the repaired pleura defect during a Valsalva maneuver. The red rubber catheter is placed in a low water-sealed suction apparatus with 20 mL of water pressure applied. Once a chest X-ray shows the pneumothorax to be resolved, the tube is removed and an occlusive dressing is placed over the wound. The tube can usually be removed in the recovery room.
- In shaping the ribs at the recipient site, exaggerate the contour to allow for the resorption that will naturally occur.
- In female patients, the best exposure for taking the rib is through an inframammary incision. Such scars are well hidden and heal nicely.

Despite the usefulness of rib grafts, given the problems with resorption and the “washboard” effect that can occur with lattice-type reconstruction, this technique should be reserved for those cases in which skull bone is not available. It has been our experience that the rib grafts look best in the initial 2 to 3 years; by 10 years after repair, the aesthetic outcomes can be much less gratifying.

Iliac Crest Bone Grafts

The iliac crest has always been used by neurosurgeons as a donor site, historically in connection with anterior cervical discectomy. A fair amount of bone can be obtained—usually without entailing significant morbidity. The patient’s most common complaint is of pain at the belt level postoperatively. The major problem with iliac crest bone is that the available bone is limited in quantity and possesses minimal contour. Despite these reservations, the iliac crest still remains an adequate source of bone in situations in which skull bone or rib is not available (► Fig. 58.13).

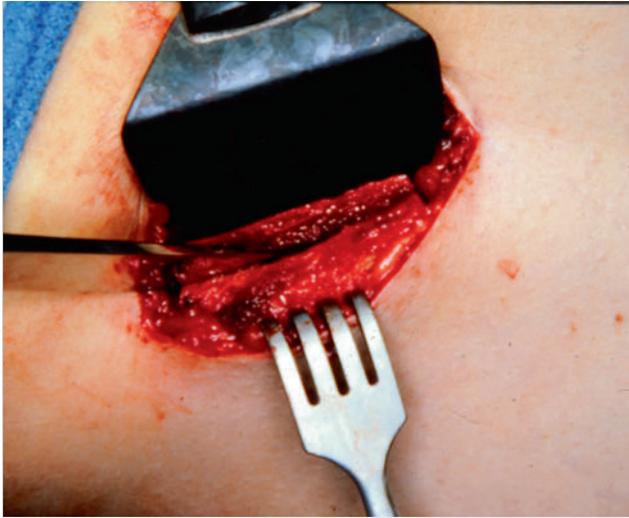


Fig. 58.13 Harvesting an iliac crest bone graft. The iliac crest is exposed, and the split graft is lifted out.

To harvest iliac bone, the iliac crest is identified. A linear incision is then made 1 to 2 cm “below” the crest. Avoiding the crest location reduces excessive scar formation and, more importantly, the “belt level” pain plus scar, which can be quite debilitating. The incision is carried down through the subcutaneous tissue to the muscle. The aponeuroses of the internal and external oblique muscles are incised, and the transversalis fascia is exposed. This fascia is then excised from the internal table of the iliac bone. The abdominal contents are retracted medially. If the subperiosteal plane is followed, up to 4 to 5 cm of iliac crest can be exposed. With osteotomes and an oscillating saw, a premeasured unit of bone is harvested. The site is then packed with Surgicel (Ethicon, Somerville, NJ) or Gelfoam soaked in thrombin. Large emissary veins do sometimes occur in the bone, and these can be controlled with bone wax. A closed Jackson-Pratt drain is tunneled subcutaneously away from the surgical site and removed after 24 hours. Fascial layers are reapproximated and closed and a multilayer closure accomplished. Iliac bone is cancellous, like calvaria, and is less likely than rib to resorb. Iliac bone revascularizes much more rapidly than rib, leading to a quicker incorporation into the surrounding skull bone. The disadvantages are mainly that iliac bone is more brittle, less malleable, and more difficult to contour than rib. Iliac crest bone is not a good source for grafts to be used in regions such as the vicinity of the orbit, in which aesthetic contouring is important. This technique is also age-dependent; it should not be used in children younger than 5 to 6 years.

Summary of Autologous Bone-Grafting/ Cranioplasty Techniques

In order of preference, bone is harvested from the following sources:

- Cranial bone
- Rib
- Iliac crest

Cranial bone clearly has the most advantages; it is typically close to the operative site and offers different contours along with often-needed generous portions of bone. A second incision is not required, and secondary resorption is minimal. Ribs are a good secondary source when calvaria is not available. Ribs can be split, and their innate malleability provides good contouring. When using rib, one also has to keep in mind its disadvantages, which include resorption and “washboard” effects that can develop as the child ages. Pneumothorax and painful incision sites can add further morbidity at the harvest site. A tertiary source of bone remains the iliac crest. Because it is cancellous, it is not resorbed to the same extent as rib. However, its lack of contours and brittleness make an aesthetically acceptable repair less likely than when rib or calvaria is used, particularly around the orbits and forehead.

58.2.3 Use of Implantable Cranioplasty Materials for Cranioplasty Reconstruction

Over the years, neurosurgeons have searched for the ideal material for the repair of bony defects in the skull. The ideal characteristics of implantable materials for use in reconstruction of the calvaria were outlined by Firtell and Grisius¹⁶: (1) inertness, (2) malleability, (3) availability, (4) radiolucency, (5) sterility, (6) durability, (7) nonconductivity, (8) biocompatibility, and (9) low cost. In the infant and child, another important factor is (10) the ability of the material to grow with the child.

Beginning in the late 1980s, our neurosurgical service made significant strides in avoiding the use of foreign materials in the growing child. Over the years, it has been a rare occasion when we are not able to find autologous bone for the repair of skull and facial/orbital bone. Metal implants conduct heat and cold, and patients were often bothered by them, especially during weather changes. Belloste pointed this out in 1713⁸ in connection with a child in whom he had placed a lead craniotomy plate. Acrylic resins have been popular over the last several decades for cranioplasty; however, it must be remembered that these materials are not incorporated biologically and hence always remain “foreign.” Often overlooked is the concept that these materials do not grow with the child and can over time become “floating islands” in the skull. Furthermore, foreign materials of any type degrade with time and always entail an increased risk for infection. Probably most disturbing to the pediatric neurosurgeon (and family!) is the return of a child several years after repair whose implant material is now free-floating (i.e., no longer in contact with the calvarial margins) and providing none of the desired intended protection and stability. However, for the sake of completeness, some of the cranioplasty materials available to the neurosurgical community are discussed, with a focus on their pros and cons.

Methyl Methacrylate

Methyl methacrylate (MMC) is among the most commonly used cranioplasty materials in the neurosurgical community.⁴¹ When combined with a wire mesh or titanium plates, it

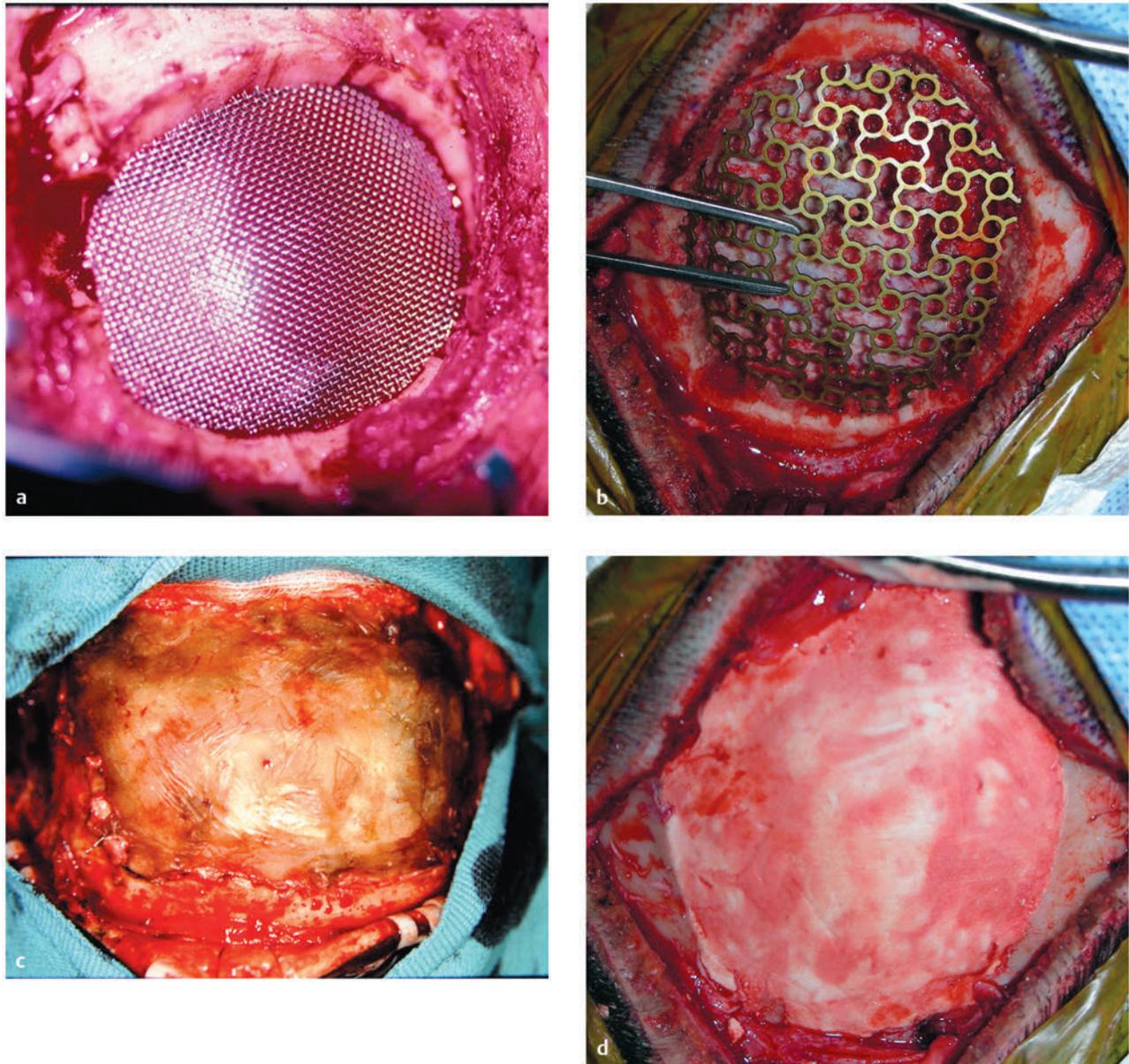


Fig. 58.14 (a) A wire mesh template has been placed into the debrided craniotomy site. (b) A titanium mesh plate is contoured and placed into the defect, with enough distance allowed over the top in which to place the implant material. (c) Methyl methacrylate has been applied over the mesh material, with the material contoured to the skull surface. (d) In this case, a “bone source” material has been layered over the mesh to provide the necessary contour.

becomes durable and malleable and can be shaped as needed. The technique for constructing an MMC implant is straightforward. The graft site is prepared as described above. The bone edges are freshened and any fibrous material removed from the bone edges. The bone edges should be bleeding slightly, with any heavier bleeding controlled with Avitene or Gelfoam (not bone wax). If dural tears are noted, they must be sutured and closed. The ends of the bones surrounding the defect are given a “step-off” edge with a squared-off bur tool attachment. It is on this bone ledge that the contoured wire mesh is placed. The step-off along the bone edge is a key design because the ledge prevents the wire mesh from slipping and penetrating into the

dura. This is particularly important in active children subject to falls during play. The mesh is shaped and designed to match the prevailing contour of bone but placed slightly lower to allow for the layer of MMC that will be placed over the mesh. If possible, the wire mesh should be made of titanium rather than stainless steel because titanium is stronger and less susceptible to deformation with direct impact. With the increased use of magnetic resonance imaging and computed tomography (CT), titanium causes less metallic artifact on scanning. However, in many parts of the world the cost of titanium is prohibitive, so the cheaper stainless steel mesh is still commonly used (► Fig. 58.14).



Fig. 58.15 (a) A 6-year-old girl had had a methyl methacrylate (MMC) plate placed 2 years previously. The plate became infected and over time was exposed. Here, necrosis of the overlying skin flap can be seen, with active purulence and exposure of the acrylic and wire mesh underneath. (b) The MMC implant was removed. No incorporation of the plate had occurred, and the wire mesh edges had eroded through the skin. The implant was removed and split calvarial bone grafts were placed. With a now 25-year follow-up, the grafts have survived well. (c) The patient 6 months after a split bone graft repair, with the original wounds well healed. We have followed this patient now for 25 years, and the grafts have remained stable.

MMC is provided as a powder and a liquid catalyst that are mixed to form a paste having a putty-like consistency; if applied when too liquid, it will run off the field. Using a moistened gloved finger and paying close attention to desired contours and height, the surgeon applies the paste in layers. Any rough edges are smoothed out before the material sets. Extra effort is needed to be sure that none of the edges of the wire mesh are exposed; failure to cover these edges can lead to erosion through the skin or penetration of the dura. As the MMC dries, it becomes extremely exothermic, so constant cool irrigation must be applied until the flap is completely dry; otherwise, the heat can injure the dura and underlying brain. A useful technique is to take a 5- to 6-cm ball of the MMC paste and hold it in one hand while irrigating the plate; by gauging the temperature of the paste as it sets, one can determine the stage of the setting process of the paste and how much heat is being generated in situ. Once the MMC has completely set, examine and remove any rough or sharp edges. These rough edges are easily removed with a high-speed round bur before closure. Before skin

closure, vigorous irrigation of the implant site is important to remove any remaining dust and debris.

In early reports of a large series of MMC cranioplasties, Rish et al¹⁹ documented a low incidence of infection (3.7%) and a low rate of cranioplasty loss (3.1%). However, a review by Blum et al²³ revealed that over the long term (i.e., more than 8 years, especially in the pediatric population), the failure rate becomes much higher; these investigators reported a 23% complication rate. In our own personal experience, as you reach the 20-year implant time, the combined risks for infection, extrusion, migration, and sinus tracts approach 80%. In the growing child, MMC is a foreign material, and its failure to grow with the child makes for a very undesirable situation. The exception is those rare situations in which there is not enough native autologous material, and then an MMC plate can be placed as a temporizing measure. As the child gets older and more autologous materials become available, the foreign plate can be removed and replaced with native material (► Fig. 58.15).

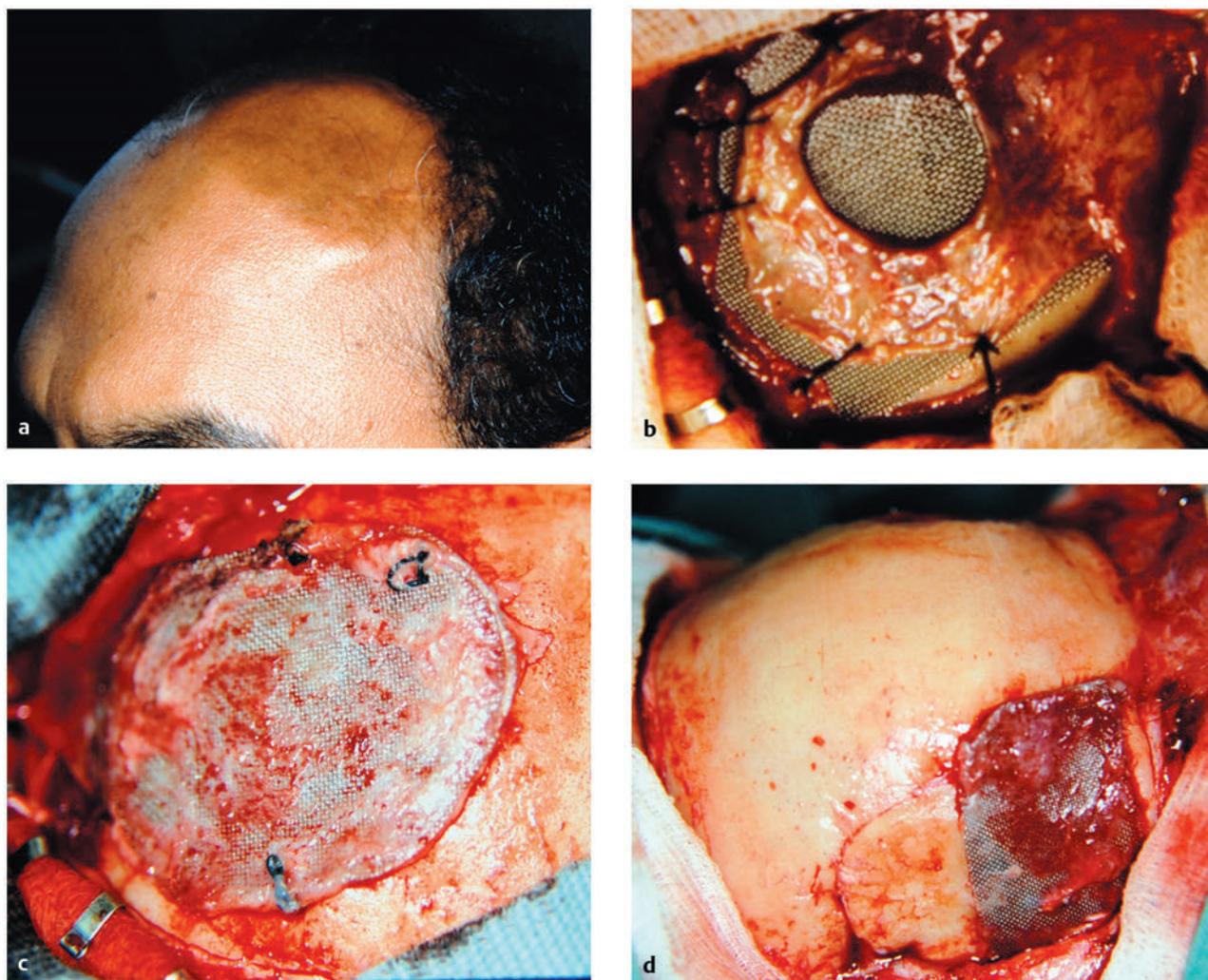


Fig. 58.16 (a) This patient had a wire mesh placed for a posttraumatic defect and presented 16 years later with a flattening of the implant after a minor blow to the head. (b) Multiple wire mesh implants were placed for posttraumatic defects. Eighteen years after placement, the mesh began to migrate into unacceptable positions over the skull. (c) A wire mesh cranioplasty was placed in the forehead for a traumatic skull injury. The patient developed a late-onset infection 12 years after placement of the wire mesh implant. (d) A mesh implant was placed in the right side of the forehead after a craniotomy flap infection. The patient presented 16 years later with the mesh eroding through the skin.

Other Cranioplasty Materials

Hydroxyapatite

Over the years, manufacturers have proposed a number of substitute materials as the “ideal” bone replacement. Although the initial results were encouraging, with time these materials gave rise to the same problems described above: resorption, infection, erosion, fracture, and extrusion. A material originally developed for use in maxillofacial surgery is hydroxyapatite, which is derived from native sea coral that is triphosphorylated under high pressure, then reaminified to form a matrix resembling that of bone.^{42–47} The concept was that when the reformatted hydroxyapatite was placed within a region that had bone, the matrix would be filled by an ingrowth of native osteocytes, blood, and bone marrow matrix. In other words, it was hoped that there would be natural osseous induction and osseous conduction into the hydroxyapatite. Studies by

Holmes and Salyer originally demonstrated up to 30% replacement with *in vivo* osseogenesis and osseous conduction.⁴² With the introduction of CAD/CAM (computer-aided design and computer-aided manufacturing) equipment, CT-designed units could be ordered that were premeasured to fit a craniofacial defect.⁴³ The theoretical advantages of this material led to initial enthusiasm. No donor graft was required, contoured pieces could be obtained, and the ingrowth of native bone substrates appeared to make this material ideal for the growing child. In reality, surgical experience in humans has shown that these ideals have not been realized in the same fashion as was seen in animal models. In the early 1990s, we had several cases in which this material was used, and unfortunately we had a 100% failure rate. In its reconstituted form, hydroxyapatite is hard to shape and extremely brittle—rendering it more susceptible to fracture and dislodgment in children.

A different formulation of hydroxyapatite material has been available in a paste format (e.g., Norian Craniofacial Reconstruction System; Synthes Maxillofacial, Palo Alto, CA; BoneSource; Stryker Leibinger, Porage, MI; Minix; Biomet, Warsaw, IN) The material is provided as a powder that, when mixed with a catalyst solution, forms a putty-like material.^{46,47} The paste is amenable to easy contouring and placement into defects. Our craniofacial team initially used this material for contouring and filling in trauma defects, especially around the orbits. However, having now followed these patients for 15 or more years, we have found higher than acceptable infection rates, along with skin extrusion. In several cases of reoperation, we noted an almost complete lack of bone conduction and integration. We also noted that with time, the paste tended to return to a powder form. In cases in which the paste was used to “contour” a surface, it formed only a veneer that with just mild trauma could easily be fractured. Postoperative seromas have also occurred around the implant material. With the present formulations, we do not share the enthusiasm of our plastic surgery colleagues for these bone cement/paste materials and have given up their use in our craniofacial reconstructions (► Fig. 58.17). The current recommendation is for the limited and selective use of these bone “replacement” products in the pediatric population.

Porous Polyethylene (Proplast I and II)

Proplast (a polymer of polytetrafluoroethylene and carbon filaments) been used extensively for years by our colleagues in maxillofacial and oral surgery. Its utility in craniofacial and trauma surgery has yet to be determined.^{48,49} The porous matrix is designed to allow ingrowth of the host's tissue and osteogenic and vasogenic material. Proplast I is made from a black porous carbon with added Teflon. Proplast II is a white carbon material to which Teflon and alumina have been added. Both types of Proplast are chemically inert, biocompatible, nonallergenic, and approved for implantation. Pore sizes range from 50 nm to 400 nm. The material is produced in a number of shapes and sizes. The proposed advantages of Proplast are several: (1) It can be carved to any desired shape and size; (2) with time, a fibrous vascularized tissue grows into the material and rapidly becomes stabilized next to the adjacent bone or soft tissue; (3) Proplast has been used extensively in the periorbital, nasal dorsum, zygomatic, and malar regions with good results. Our team has used it on occasion to fill defects of the calvaria in young children during craniofacial repairs in which opportunities for harvesting bone grafts were limited. With time, the material has been shown to have several disadvantages: (1) Because fixation to adjacent tissue takes time, Proplast can migrate; (2) if used in the very young child, Proplast does not become contoured to the surrounding structures as the child grows, making for a potentially unacceptable aesthetic result. Its use in the younger pediatric population (i.e., younger than 12 years of age) and the fact that it is being placed in children with normal, long life expectancies tends to give considerable thought before placing it in a child (► Fig. 58.18).

Silicone and Silastic Implants

Silicone has been used widely in craniofacial reconstruction.^{50–52} It is inert and well tolerated by the body, evoking only a rare

local inflammatory or allergic response. Silastic (Dow Corning, Midland, MI) implants are now available in various sizes and preformed shapes. The material is easily shaped or carved in the operating room; in the face, the aesthetic results initially can be quite good. However, with more than 25 years of experience, we have discovered that there are some significant disadvantages (► Fig. 58.19).

- With the passage of time, this material, particularly in growing infants and children, has a tendency to migrate and come to rest in less-than-desirable locations. Once placed, the implants do not withstand trauma well and can be displaced as a result of a blow to the head or face.
- In growing children, the material can eventually lose its contour to the surrounding structures.
- As an implanted foreign material, it always remains susceptible to infection.

Cadaver Bone

The use of cadaver bone as a cranioplasty material is long-standing. In principle, cadaver bone is supposed to provide a matrix for new bone ingrowth. In reality, this rarely occurs, or at least the ingrowth of bone remains restricted to the outer margins of the implant. Most sources of cadaveric bone have been freeze-dried, chemically treated, or irradiated. Unfortunately, these treatment techniques cause a severe denaturation of base proteins, increasing significantly the risk for rejection and resorption. Only in total cranial reconstruction, in which the amount of bone required far outstrips donor sources, are the advantages of cadaver bone likely to outweigh its disadvantages.

58.2.4 The Future: Craniofacial Tissue Engineering

In the pediatric population, the use of “nongrowing,” non-biological metallic and bioceramic implants have so far led to very undesirable long-term results. So, in the future, research is likely to look into the production of natural or enhanced materials that are both *osseous-inductive* and *osseous-conductive*. Efforts in tissue engineering began in earnest in the early 1990s, and owing to the worldwide incidence of congenital defects, oncologic disease, and trauma involving the craniofacial region, much work has been directed toward the biological regeneration of skin, cartilage, and bone.^{43,47,53–56} With stem cell research becoming more realistic and productive, it is hoped that all of these technologies will solve many of the problems we have today in finding biologically long-lasting repair materials for pediatric (and adult) populations.

58.3 Management of Scalp Lacerations

Scalp injuries are very commonly a concurrent injury with a skull fracture, and the neurosurgical team needs the skills to deal with both. Scalp injuries can range from simple abrasions requiring minimal care to extensive scalping injuries with total

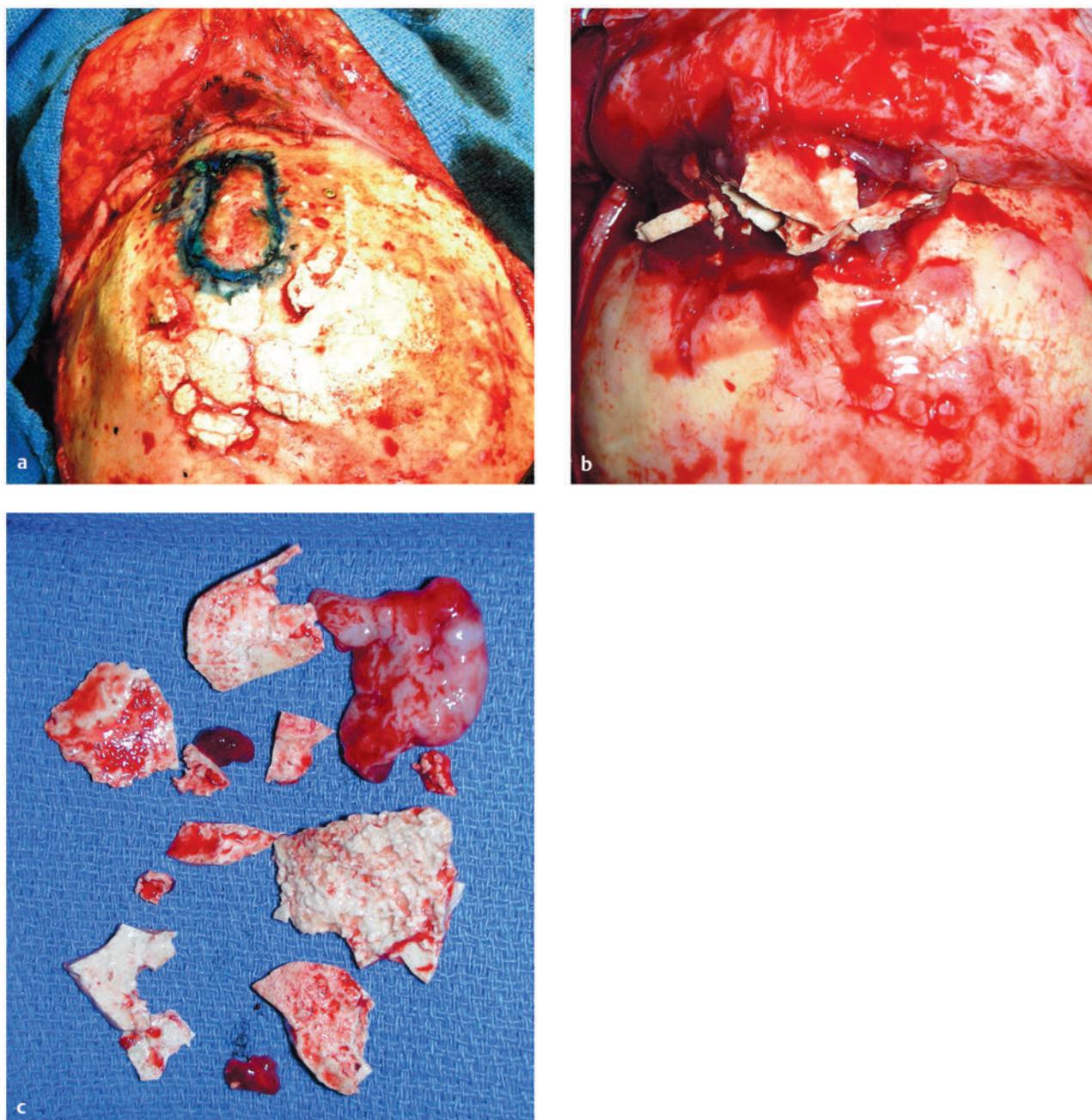


Fig. 58.17 (a) A child who as an infant had a craniectomy for metopic synostosis. The shape of the head was “normalized” with an onlay bone paste. The child presented 4 years later with a persistent pulsatile defect of the forehead. At reoperation, the bone paste was found to be only an onlay veneer that easily chipped off—there was no osseous integration. (b) A child who had a frontal region defect filled and contoured with a bone paste. The patient presented to us after mild facial trauma, with the paste fractured into pieces and totally disrupted from the defect site. (c) From a patient in whom a bone paste material had been placed to contour and smooth out several skull defects. The child presented later with the material infected and in a couple of places extruding through the skin. The paste had formed only a veneer and was easily chipped off the underlying bone.

scalp loss. Since the advent of the industrial revolution, society has become quite inventive in discovering new ways to injure the head and scalp. Each of the major types of injuries requires its own management regimen. It is the purpose of this section to review some of the surgical techniques available to the neurosurgeon (often in cooperation with our colleagues in plastic surgery) for the care and management of scalp injuries in the pediatric population.

58.3.1 Anatomy of the Scalp

An understanding of the anatomy of the scalp is a prerequisite for the repair of scalp lacerations of any type. A simple mnemonic, SCALP, still used by medical students, is helpful in recalling some of the salient points of scalp anatomy (► Fig. 58.20).

(See box “Meaning of the Mnemonic SCALP (p. 772).”)

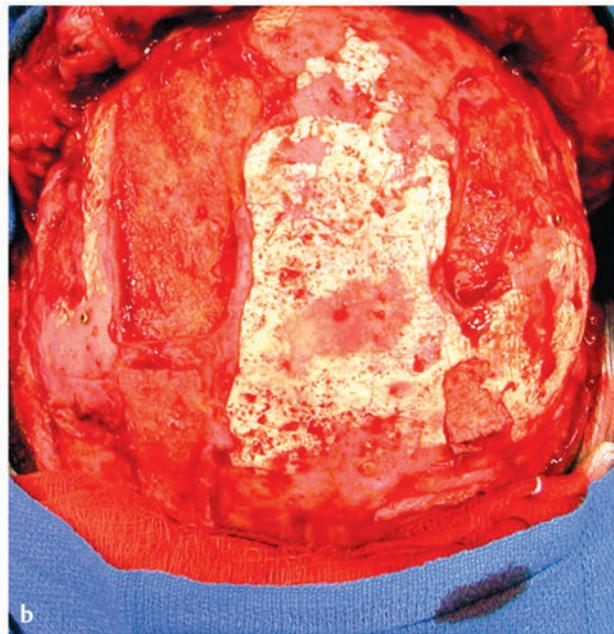
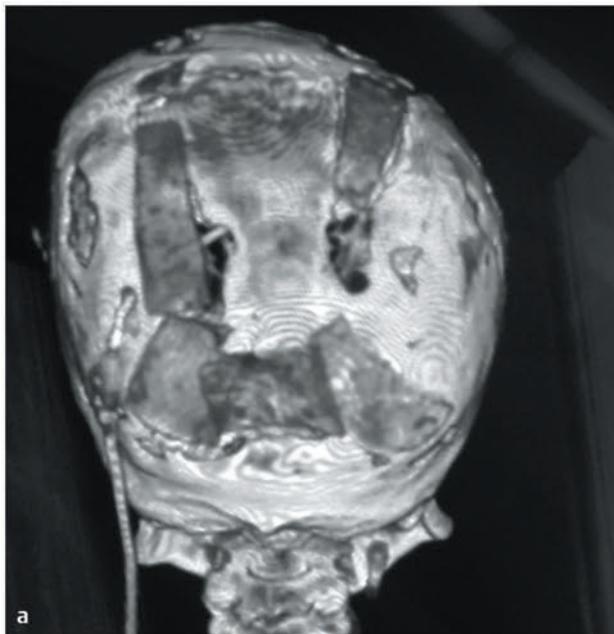


Fig. 58.18 (a) A three-dimensional computed tomographic (CT) scan of a teenager who had Proplast placed as an infant for a craniofacial reconstruction. In this CT scan, the blank areas of bone are where the Proplast was placed, and there is a clear lack of osseous integration, with large persistent bone defects still present. (b) A view of the top of skull of a patient in whom Proplast (lateral and midline placement) and bone paste were used for calvarial reconstruction. The patient presented 5 years after the bone paste had been placed for contouring with erosion of the material through the skull. As in the case shown in ► Fig. 58.16c, the bone paste easily chipped off, like a surface veneer. (c) Proplast sheets after removal and upon examination showed neither osseous conduction nor osseous integration. The material essentially acted as “onlay” graft.

Meaning of the Mnemonic SCALP

- Skin: the outer, hair-bearing portion of the scalp containing the dermis and epidermis. Aesthetically, it is the most important structure in any repair.
- Connective tissue: a thick subcutaneous layer of fat and connective tissue that attaches the skin to the underlying galea. Within this layer are nerves, arteries, and veins and the lymphatic system, all linked in a key network of anastomoses.
- Aponeurotic tissue: also called the epicranium or galeal layer. This is the fascial plane connecting the frontal and occipital muscles.

- Loose connective tissue: a layer of tissue between the aponeurotic layer and the pericranium. Its importance derives from the mobility it gives the scalp and from the fact that it is largely avascular, making it a useful plane for dissection and the elevation of scalp flaps.
- Pericranium: also called the periosteum of the skull. This layer is densely adherent to the cranial bones and contains their vascular supply. It is anatomically crucial in many of the repairs to be described. It figures importantly in repairs or reconstructions involving the face and anterior fossa and forms the foundation for skin grafts.

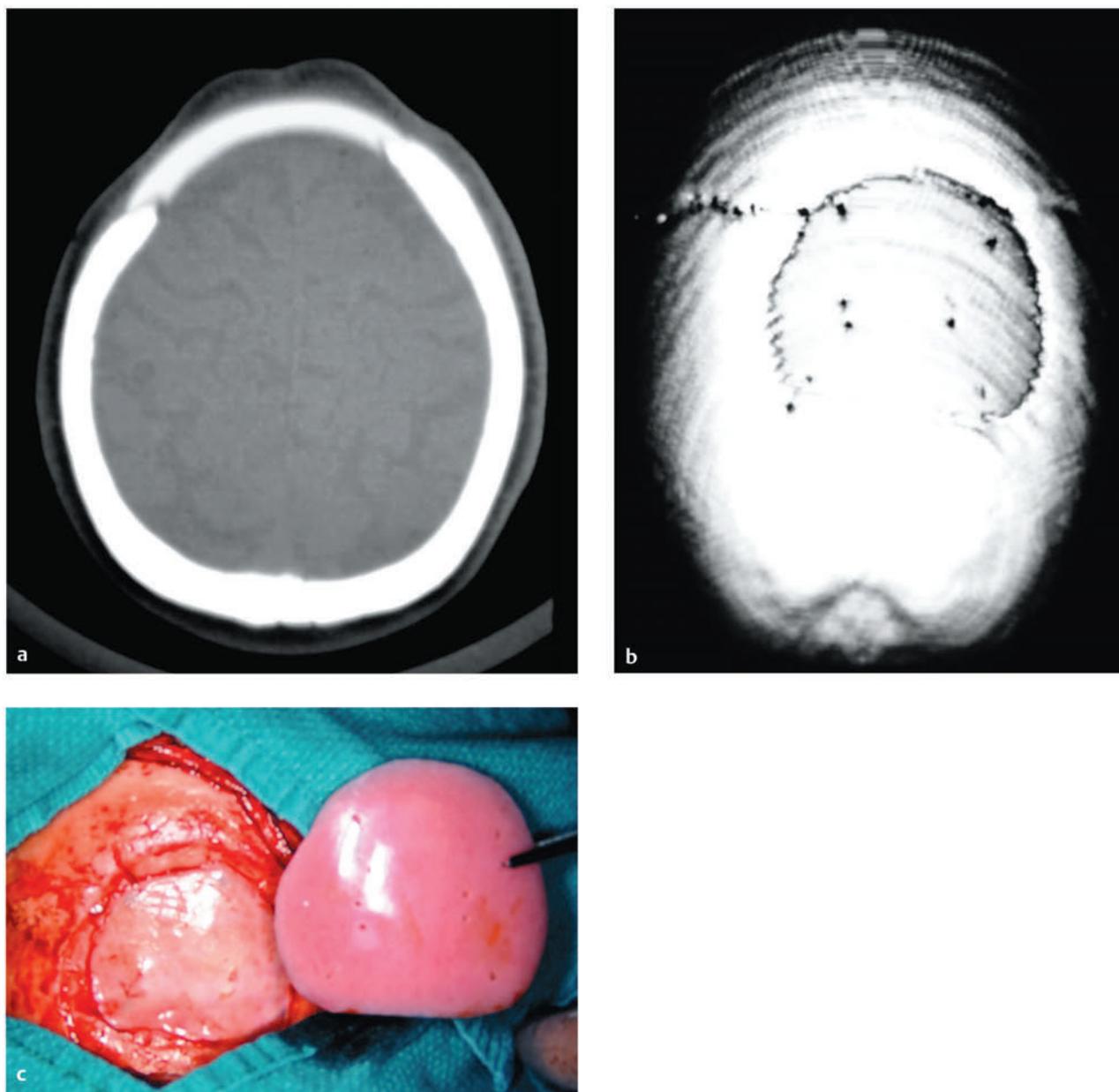
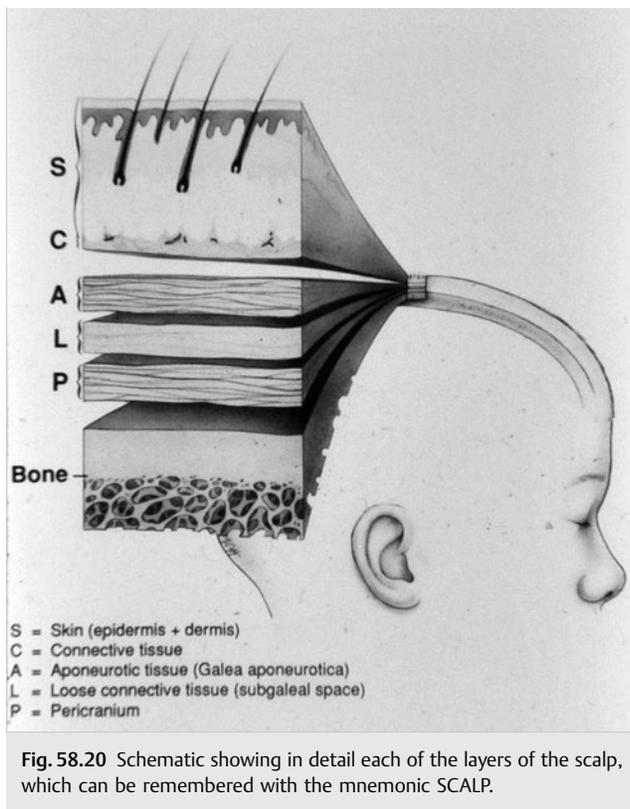


Fig. 58.19 (a) Axial computed tomography (CT) with bone windows showing a Silastic CAD/CAM (computed-aided design/computer-aided manufacturing) graft that was custom-molded for a traumatic defect. The graft shows no surrounding integration with the bone. After a blow to the patient's head 5 years following implantation, the graft became mobile. (b) Three-dimensional CT showing the Silastic implant and the clear lack of surrounding integration with the skull bone. (c) At surgery, the Silastic implant was found to "free-floating," with no attachment to the surrounding bone; there was actually loss of bone at the interface of the graft and the bone. A Silastic foreign body membrane had formed on the dural surface.

58.3.2 Vascular Anatomy of the Scalp

The scalp is essentially an end vessel in the vascular system. Twenty percent of the cardiac output is supplied to the head and neck. As a result, the bleeding associated with scalp lacerations and facial trauma can be massive and potentially lethal if not controlled. Fortunately, the scalp vascular system is a rich arcade with a large, overlapping anastomotic network. This overlapping system is so efficient that even a unilateral injury can be fed by the contralateral arterial network, leading to rapid blood loss.

The blood supply to the scalp is an extensive network, with a multiplicity of anastomoses evident. The main vessels include the superficial temporal (with two branches, frontal and parietal), the supraorbital, the frontal, the posterior auricular, and the occipital arteries. This network is anatomically constructed in a ringlike fashion at the base of the skull to supply the head and scalp. An appreciation of the general anatomy of the main trunks is key to understanding the basis of any successful flap rotation or repair of scalp lacerations.



58.3.3 General Principles

The basic principles of wound care are summarized by the mnemonic HEDSAT (see box “HEDSAT (p. 774)”).

HEDSAT

- Hemostasis
- Examination of the skull
- Débridement
- Skin closure without tension
- Antibiotics
- Tetanus prophylaxis

Because scalp injuries can hemorrhage extensively, the early control of bleeding is essential. In an emergency situation, this is readily accomplished with the application of pressure to the wound edges. Once hemostasis has been obtained, débridement and cleaning of the wound are necessary to reduce the risk for bacterial contamination (a useful rule of thumb is a bacterial count of less than 10^5 per gram of tissue). With a sterile gloved finger, the surgeon examines the skull for a defect or fracture.

Once cleaned and debrided, the wound is closed according to one of the cardinal principles of wound care: **closure without tension**. Wounds closed under tension are at high risk for breakdown, and in addition, undesirable scars will form secondary to wound separation. Techniques to reduce wound tension are discussed in a later section of this chapter.

In children up to the age of 10 years with up-to-date immunizations, the tetanus prophylaxis given with their diphtheria-pertussis-tetanus shots provides adequate protection. In older

children, past the age of 10 years, a tetanus booster will be needed if the wound is contaminated. Antibiotics are often given to children with contaminated wounds; simple, clean lacerations rarely require coverage. Potentially the most serious wounds are typically seen in the abused child afflicted with a human bite. Animal bites are often seen in emergency departments and also require aggressive treatment with antibiotics.

Most injuries encountered in the pediatric emergency department can be managed with local anesthesia. For children with extensive scalp injuries, it is more reasonable to use general anesthesia and carry out the surgical procedure in the operating room, often in collaboration with our plastic surgery colleagues.

58.3.4 Treatment of Common Scalp Injuries

Skin Abrasions

The skin abrasion is the most common injury, but it is in most instances cared for by the emergency department staff and rarely called to the attention of the neurosurgeon. If the dermis is intact and only abraded, local wound care is provided. It is most important to remove any in-driven dirt or particles that can later tattoo the skin. Occasionally, dermabrasion or coarse brushing of the dermis will be necessary; this is usually done with the patient under general anesthesia.

Skin Lacerations

Simple skin lacerations are managed by achieving hemostasis, performing routine débridement, and aligning the skin edges. Two-layer closures are rarely necessary in children except in the instance of the forehead and periorbital region, where skin sutures are removed early to reduce scarring; two-layer closure allows early suture removal. On our service, we routinely make a two-layer closure; undyed sutures are used in the subgaleal layer (dyed sutures can tattoo the very young child's skin) and fine nylon sutures (5-0 or 6-0) for skin closure; the nylon sutures are removed at 5 days. Suture placement must be meticulous and approximation of the skin edges perfect. Inadequate attention to detail makes for poor wound closure (resulting in a higher rate of infection) and disgruntled parents. Staples are inappropriate for wound closure on the face or forehead region and also inappropriate for the young child (younger than 7) because only one size—adult—is available and so provides poor skin approximation. The use of subcuticular absorbable sutures for the skin closure is desirable. Absorbable sutures do not require later removal (as would be the case with nylon material), thereby reducing further emotional trauma to the younger child.

Scalp lacerations are often accompanied by injuries to aesthetically important parts of the face and ears. In particular, it is important to line up the helical rim of the ear and the gray line of the eyelid so as to restore correct anatomical relationships; if this is done inadequately, the aesthetic outcome can be dismal. At the same time, attention must always be paid to the potential skin stretching that can distort adjacent structures. For example, in a patient with a forehead laceration that causes tissue loss, stretching the scalp to close the wound can potentially distort the face, a situation rarely acceptable to the patient or

parents. In children, as opposed to adults, there typically is less excess skin to mobilize.

In any laceration, the primary goals should always be hemostasis, débridement, and wound closure that restores the anatomical relationships as close to normal as possible.

Contaminated Scalp Lacerations

In a patient with heavily contaminated scalp lacerations, the surgical team should consider a delayed secondary closure. Bites inflicted by humans or animals and wounds contaminated with dirt (as in injuries caused by farm machinery or by motor vehicle accidents in which the child is ejected from the car) are included in this category. In these situations, it is often better to leave the wound open and apply frequent wound care for approximately 48 hours. Our team typically cleans the skin and debrided area with an antibacterial soap and Betadine paint. The goal is to achieve a bacterial contamination level that allows a primary closure (i.e., a bacterial count of $<10^5$ per gram of tissue). A swab wipe of the wound suffices to enable a bacteriology laboratory to obtain the desired organism count.

58.3.5 Treatment of Scalp Injuries with Loss of Tissue

In scalp injuries with a loss of tissue, the surgeon must keep a number of general principles in mind while mapping out the repair. (1) Aesthetic considerations always have to be taken into account in any tissue mobilization. (2) Therefore, if possible, hair-bearing scalp is mobilized and used in the repair. (3) Whenever a flap is rotated, especially a split skin graft, the rotation must be from pericranium to pericranium. (4) Preservation of the circulation in the design of the flap is critically important. Always include a major feeding vessel in any large flap rotation. (5) Caution must be exercised when electrocautery is used because heat or burn injury to hair-bearing cells can result in alopecia. Some of the newer cautery devices are now using a far-infrared radio-frequency current, which delivers much less heat and thermal injury to the wound edges.

Partial-Thickness Avulsion Loss of Scalp

Partial-thickness scalp loss can be treated in various ways. The particular technique that is chosen depends on the surface area of scalp that is lost and the extent of the injury. We review here some of the techniques that can be used by the neurosurgical team, often in collaboration with our plastic surgery colleagues.^{57,58}

Advancement Flap

In a partial avulsion of tissue with the pericranium intact, a simple technique is to elevate a flap of full-thickness scalp adjacent to the injury and then make radial cuts in the galeal layer, which will allow the scalp to be “stretched” to cover the defect. The incisions in the galeal layer are made parallel and 3 to 5 mm apart. The cuts **should not be made deep enough to**

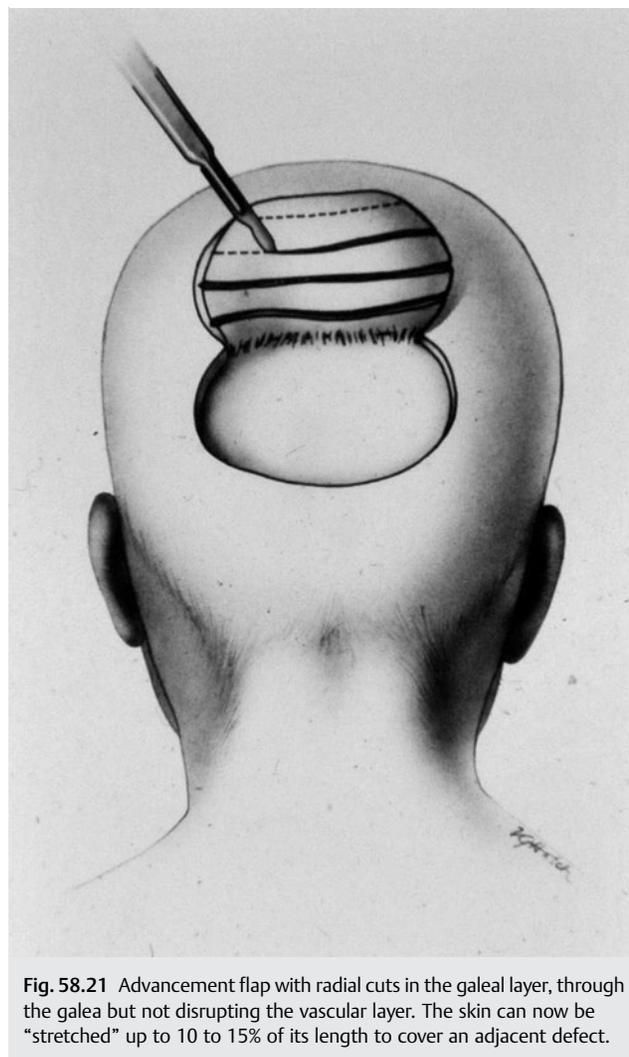


Fig. 58.21 Advancement flap with radial cuts in the galeal layer, through the galea but not disrupting the vascular layer. The skin can now be “stretched” up to 10 to 15% of its length to cover an adjacent defect.

interrupt the vascular layer; incising the galea is sufficient to obtain relaxation. Some plastic surgeons like to make cross-hatch incisions, both vertical and horizontal, and we have noted that this additional set of cuts can result in a loss of the flap due to reduced vascularity. This technique is limited by the size of the defect (usually <4 cm in the child) and the location. Furthermore, the technique cannot be used in aesthetically sensitive areas, such as the forehead, because of the potential to distort facial structures. These types of flaps are particularly useful over the high parietal and occipital region (► Fig. 58.21^{7,59}

Transposition and Rotation Flaps

The scalp injury with a small defect of less than 2 to 3 cm can be easily managed by one of the flap transposition techniques. Two relaxing incisions are made parallel to the injury in a hair-bearing region, and then the tissue is undermined with dissecting scissors by following the subgaleal plane. These parallel incisions should be no closer than 3 cm to the wound to maintain good vascularity. With wide subgaleal mobilization of

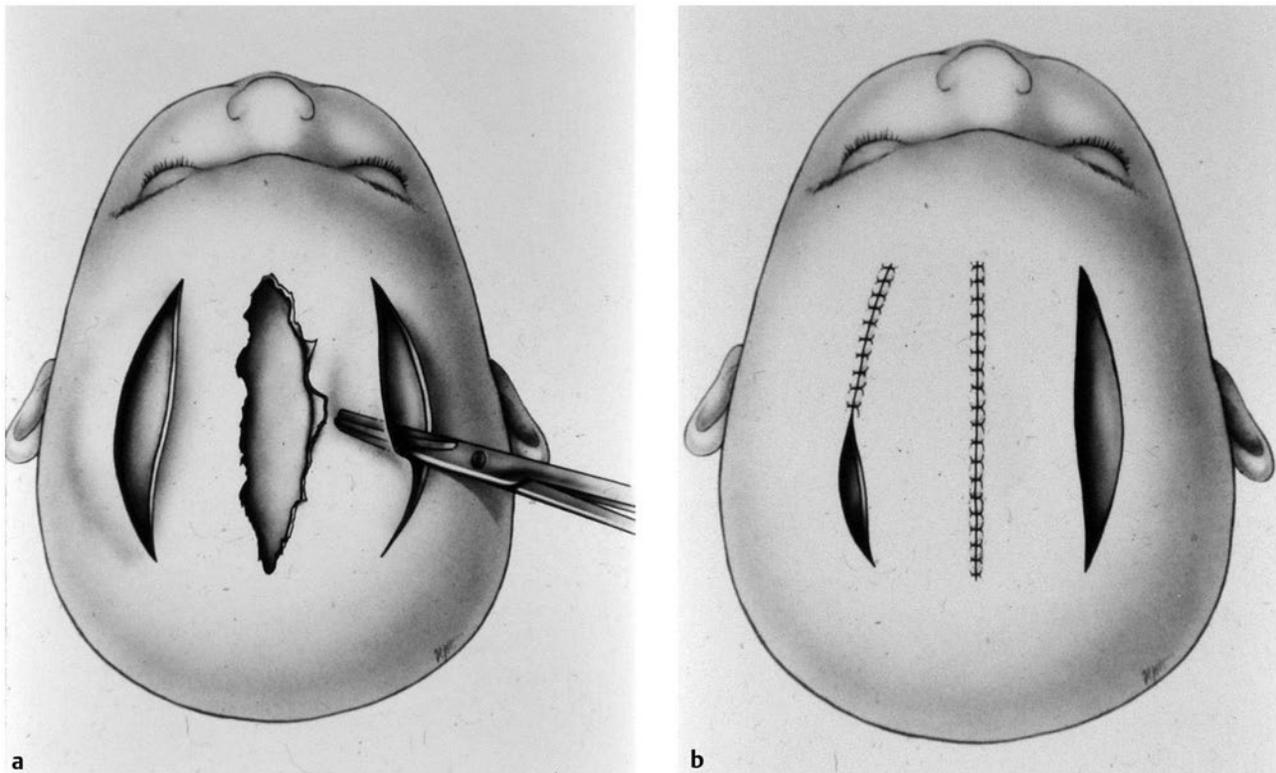


Fig. 58.22 The transposition flap, a useful technique for covering large ragged defects of the scalp. (a) With a large defect, two lateral relaxing incisions are made on each side and widely undermined. (b) The traumatic defect is closed first after the ragged wound edges have been trimmed. The lateral incisions are then further undermined to provide the necessary relaxation of tissue and skin closure with the least amount of tension possible. If the defect is so large that these maneuvers are not sufficient to reduce tension to acceptable levels, split-thickness skin grafts can always be placed in the lateral incision sites.

the skin, the initial defect is closed first primarily with as little tension as possible. The later incisions are further undermined to provide the widest degree of mobilization possible and then closed. If the extent of the transposition is too large, it may be necessary to place a split-thickness graft over the donor site to minimize tension at the wound. If such a skin graft is necessary, it can be applied over the well-vascularized pericranium, allowing a better take (► Fig. 58.22).

The Gillies tripod technique is useful in circular avulsions. The technique involves wide undermining in the subgaleal plane. The three incisions are rotated in a “tripod” fashion to the center (► Fig. 58.23).

A “lazy S-plasty” (► Fig. 58.24) is used for lateral or superiorly placed scalp defects; it is especially useful for traumatic injuries with irregular margins or in the removal of scalp lesions such as hemangiomas or neurofibromas. The flaps are elevated following a lazy S pattern; the defect is closed first, and then the suturing is extended from the center to both ends of the incision. It is not uncommon to trim the lateral margins of the transposed tissue to eliminate redundant skin and achieve an aesthetically satisfactory closure. Typically, a dog-ear is formed at the corner of the initial wound; this will mold out with time and rarely needs to be dealt with in children.

Tissue Expansion Techniques

The use of tissue expanders has revolutionized aesthetic approaches to scalp repair. A tissue expander is a silicone prosthesis that is placed into a pocket of tissue within the subgaleal space. There are a number of advantages to using this technique. With tissue expansion, one is able to develop available skin that has the same texture, color, and hair-bearing qualities as the recipient site. For aesthetic purposes, none of these qualities can be overestimated, particularly the hair-bearing qualities. Normal scalp can be expanded out to at least twice its normal interfollicular distance without showing any obvious changes in the hair-bearing areas.

The technique is straightforward and easily accomplished in the pediatric population. With the child under general anesthesia (local is not recommended in children), the prosthesis is placed in the area from which the skin flap is to be harvested. The selection of position has to be well thought out, with consideration as to whether an advancement, rotation, or transposition flap is to be undertaken. Once the prosthesis is placed into a subgaleal pocket, it is left alone for at least 3 weeks to allow the primary incision to heal well. Once healing has been accomplished, saline is injected into the prosthesis through an injection port. The prosthesis is expanded until skin tension is

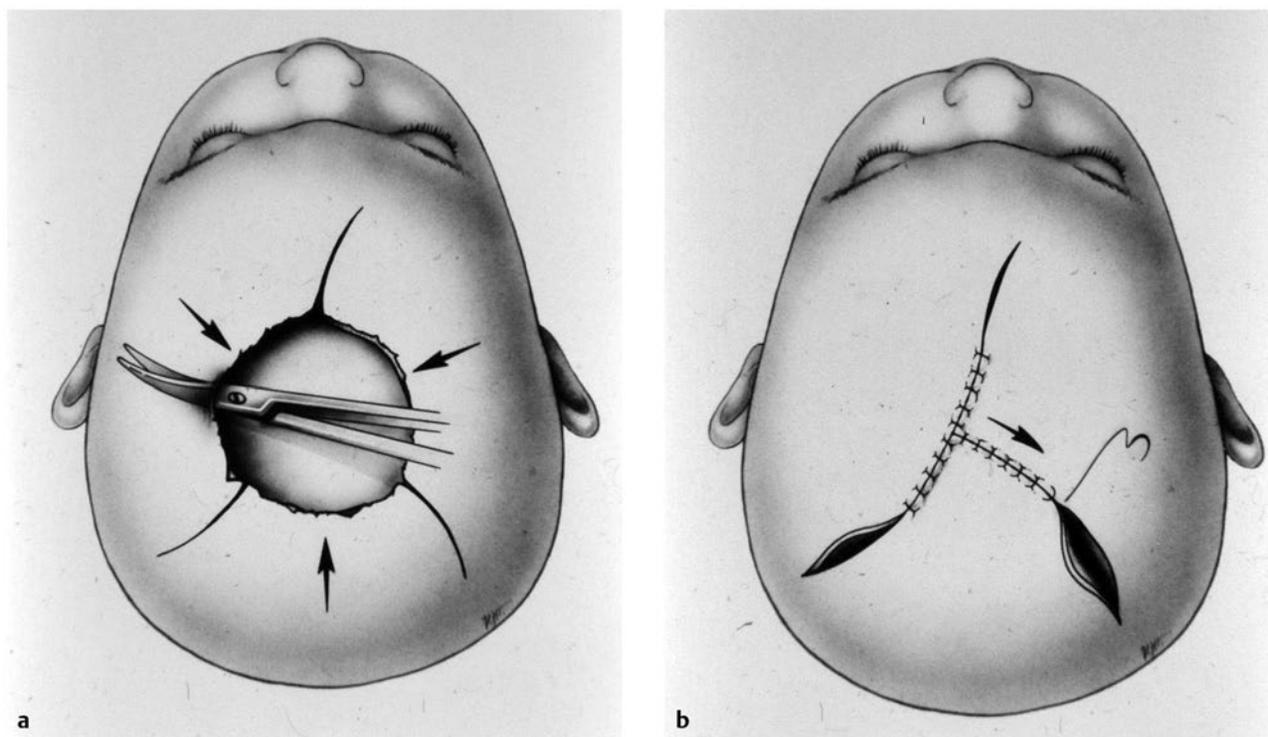


Fig. 58.23 The Gillies tripod repair, a very useful technique for closing circular defects of the high calvarial area and vertex. The arrows in (a) show the direction of the flap rotation after wide undermining of the subgaleal plane. (b) This last technique is essential for reducing tension at the wound margins.

noted. Typically, the injections are done weekly for 6 to 8 weeks, depending on the amount of redundant scalp needed. The initial 3 to 4 weeks are the most difficult for patients, especially children, but then the galea seems to relax and the expansion becomes considerably easier to accomplish. In large repairs, such as myelomeningocele flap rotations (in the older child), we have kept the prosthesis in situ for 3 to 4 months, resulting in the development of generous skin flaps. The surgeon is advised to always overexpand because typically there seems to be too little flap for the repair rather than too much. Also, at the time of expander removal, the skin, which is naturally elastic, will begin to shrink, so extra expansion is done to allow for this.

Summary for Scalp Tissue Repair

The collaboration of plastic surgeons and neurosurgeons has become a common occurrence in the operating room. As a result, the potential for the repair of complex scalp defects and complex myelomeningoceles has increased significantly. The neurosurgical team that understands the relevant anatomy and principles underlying the various rotations can perform many of these repairs. In more complex repairs, collaboration with the plastic surgeon will be beneficial. Careful attention to aesthetic considerations always makes patients and their families much happier and less socially stigmatized.

Pearls

- Autogenically harvested material (e.g., skull, rib, iliac crest) is normally the best replacement material to use in a cranioplasty. This type of material carries a lower risk for infection and will grow with the child.
- There is no contraindication to replacing open contaminated bone in a pediatric case of head trauma. As long as the bone is debrided, cleaned, and washed in a diluted Betadine (10%) solution, the replacement of this previously exposed bone does not appear to increase the risk for infection.
- In replacing bone, the use of rigid fixation helps reduce the resorption of bone and reduces the risk for slippage and displacement. The use of resorbable fixation plates in children younger than 3 years has proved very beneficial.
- For craniofacial reconstruction, the calvaria remains the best harvest site; calvarial bone carries the lowest risk for infection and the lowest risk for resorption, and the calvaria is the best area for finding appropriately contoured bone.
- It is best to minimize the use of foreign materials like bone wax and Gelfoam when bone flaps are replaced. Bone wax in particular reduces bone healing and can act as a nidus for bacteria and potential infection.

58.4 Acknowledgments

The author would like to acknowledge the wonderful cooperation over the last 27 plus years of his plastic surgery colleagues in the conceptual development of this chapter. These people

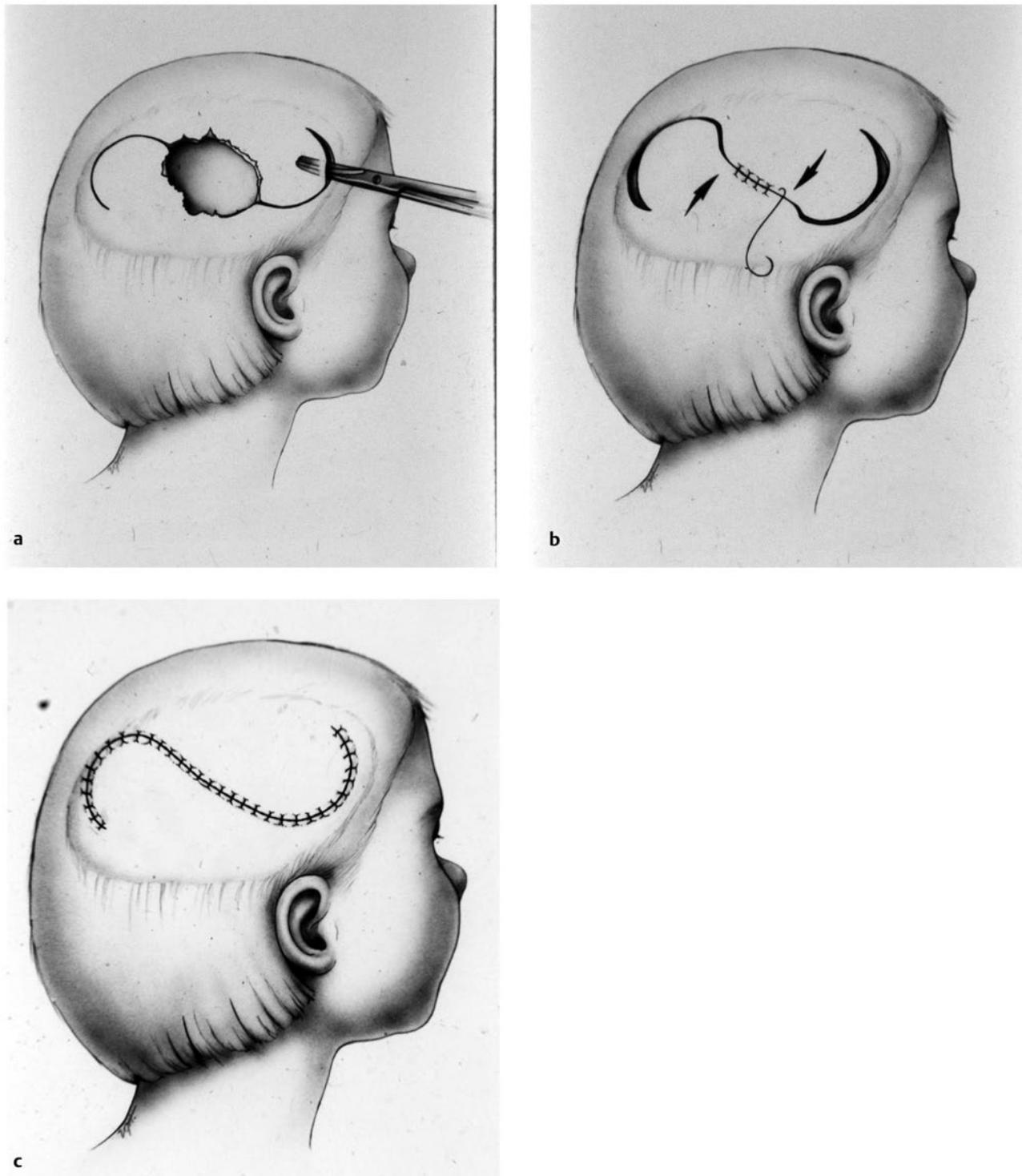


Fig. 58.24 The lazy S-plasty, a useful repair technique for larger, more irregular defects, particularly those laterally placed. (a) The curvilinear incision allows wider undermining and more flexibility in mobilizing the flaps. (b) The defect is always closed first and then the lateral margins repaired. (c) The advantage to this type of repair is the large amount of subgaleal undermining that can be done to get tissue relaxation. The lazy S incision increases the amount of skin that can be rotated.

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59 Pediatric Brachial Plexus Palsy

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Pediatric obstetric brachial plexus palsy, or neonatal brachial plexus palsy (NBPP), refers to the condition arising from a traumatic insult to one or more of the cervical roots C5–C8 and T1 preceding, during, or following the birth process. Although improvements in obstetric care and heightened attention to documented risk factors for injury have resulted in reduced rates of occurrence, the incidence of NBPP has been reported to be between 0.38 and 5.8 per 1,000 live births; an extensive epidemiologic review by Foad et al in 2008 demonstrated an incidence of 1.51 cases per 1,000 live births in the United States.^{1–3} For many children, the deficits are mild and transient, with rates of spontaneous recovery between 75 and 95% cited in the literature.^{4–7} More recent reports, however, have suggested that these outcomes may be overly optimistic, finding much lower recovery rates and significant permanent disabilities in affected patients who were managed conservatively.^{4,8–14}

In the past several decades, it has become increasingly apparent that the role of the pediatric neurosurgeon in the management of NBPP centers on the proper selection of patients for whom surgical intervention will be of benefit. This chapter reviews the anatomy and pathophysiology of NBPP, discusses the clinical presentation and comprehensive evaluation of these patients, and illustrates the current approach to the operative treatment of NBPP; the focus is on surgical timing, microsurgical techniques, treatment adjuncts, prognosis, and secondary reconstruction.

59.1 History

Although the first clinical description of birth-related brachial plexus injury was made by William Smellie in 1764, the term *obstetric palsy* was not coined until 1872. Guillaume Duchenne detailed four cases of upper brachial plexus palsy due to excessive traction on the arm and shoulder during birth, with resultant root avulsions.^{15,16} Two years later, Wilhelm Erb identified the site at which the C5 and C6 nerve roots join in the neck as the location of injury in patients with weakness of the deltoid, biceps, coracobrachialis, and brachioradialis muscles; therefore, the term *Erb* (or *Erb-Duchenne*) *palsy* refers to the classic upper brachial plexus injury involving only the upper trunk of C5 and C6 with or without C7.¹⁷ A century later, Augusta Klumpke illustrated the relationship between the Horner sign and T1 root avulsion in brachial plexus lesions; the term *Klumpke palsy*, the least common pattern of injury in NBPP, refers to an insult isolated to the lower trunk of the C8 and T1 roots.¹⁸

The first report of surgical treatment for NBPP came from Robert Kennedy in his 1903 publication describing the neurotomy resection and neurorrhaphy of the injured fifth and sixth cervical roots in a young boy with Erb palsy, and the positive results were documented pictorially.¹⁹ A subsequent review of 1,100 cases of obstetric brachial plexus palsies by Sever in 1925 concluded, however, that patients managed conservatively or surgically had the same outcomes.²⁰ In light of this finding, primary operative intervention for NBPP was rarely employed until the advent of microsurgical techniques and improved

pediatric anesthesia in the 1970s. The published works of Millei, Narakas, and Gilbert et al, each highlighting favorable results in patients with NBPP treated with direct surgical repair, rekindled an interest in the operative treatment of birth brachial plexus palsy that continues to this day.^{21–23}

59.2 Epidemiology

At present, NBPP occurs in more than 5,400 children born in the United States each year, and rates are nearly equal between male and female newborns.^{24,25} Although some authors have cited congenital malformations and uterine cavity abnormalities as possible causes of obstetric brachial plexus palsy, the presumed etiology of NBPP is difficult childbirth and the excessive application of lateral traction forces to the nerves during delivery.^{26–28} This scenario usually occurs in the setting of shoulder dystocia, in which the upper extremity is pulled in excess of nerve tolerance during extrication, or of hyperextension of the arms in a breech delivery.²⁹ Trauma to the upper roots of the plexus typically takes place in a vertex delivery with shoulder dystocia when the neck is laterally flexed with the arm in adduction to free the shoulder from the pubic arch. Because of the more common left occiput anterior presentation of the descending fetus, right-sided lesions occur more frequently; injury to the posterior shoulder, however, may occur when that shoulder is lodged on the maternal sacral promontory during the birthing process.^{26,30} Bilateral injuries have been reported with breech presentation, although unilateral insults to the upper roots are still seen more often in that setting.^{31,32} Several investigations have demonstrated that more than 1% of cases of NBPP occur following cesarean deliveries.^{33,34}

59.3 Risk Factors

Despite increased awareness of the problem, NBPP is not a preventable disease. In fact, a study by Mollberg et al showed that the incidence of obstetric palsy has actually increased in one industrialized country over a recent 10-year period.³⁵ As a result, significant attention has been paid to the identification of predisposing factors that may be associated with the occurrence of NBPP. These include maternal characteristics, such as obesity and excessive maternal weight gain, primiparity, grand multiparity, gestational diabetes, and advanced maternal age (older than 35 years); labor-related factors are shoulder dystocia, prolonged second stage of labor, vaginal breech delivery, instrument (vacuum)-assisted vaginal delivery, and epidural analgesia. The most important fetal trait is macrosomia (birth weight > 4,500 g).^{36–40} Several recent studies have determined that shoulder dystocia and the ancillary maneuvers required to deliver the shoulders are the most prevalent risk factor for NBPP, although prior reports suggested it is much less common.^{41–43} The observation that some patients with NBPP have one or more risk factors while others have none has led some investigators to hypothesize that not all permanent brachial plexus injury is due to birth-related traction, and some patients may

have an undefined or inherent susceptibility to the condition.⁴⁴⁻⁴⁶ Other traumatic lesions, such as fractures of the clavicle and humerus, facial nerve injury, cephalohematoma, and torticollis, have been associated with obstetric brachial plexus palsy.^{41,47-50}

59.4 Surgical Anatomy and Pathophysiology

Peripheral nerve injuries have been classically described and categorized, first by Seddon in 1943 and later by Sunderland in 1951.^{51,52} In Seddon's classification (and Sunderland I), neurapraxia refers to a physiologic block of nerve conduction within affected axons without a loss of axonal continuity; it is the mildest form of injury, and full recovery is generally observed in days to weeks. Axonotmesis (Sunderland II-IV) involves a relative loss of continuity of the axon and its myelin sheath, but with preservation of the epineurium and perineurium; wallerian degeneration and scar formation occur, but recovery may take place without surgical intervention if the axons successfully grow back to reach the target muscle. Neurotmesis (Sunderland V) describes a total severance or disruption of the entire nerve fiber; recovery from this injury is not possible without timely surgical treatment. Mechanically, these insults have been referred to as stretch (Sunderland I), varying degrees of rupture (Sunderland II-V), and avulsions.⁵³

More clinically relevant than pathologic severity is the anatomical localization of the brachial plexus injury. Most authors recognize four major patterns of injury, described by Narakas and others, involving three plexus palsy categories: upper, lower, and total.⁵⁴⁻⁵⁶ The first and most common is a purely upper brachial plexus lesion affecting C5 and C6 (Erb palsy) and causing weakness of only the deltoid and biceps; several reports have demonstrated evidence of rates of spontaneous recovery as high as 90% in these cases.^{57,58} The second presentation is that of an injury involving the C5, C6, and C7 roots. The arm is internally rotated and adducted at the shoulder, the elbow is extended, the forearm is pronated, and the wrist is flexed with fingers extended, resulting in the "waiter's tip" posture. The next most common type of birth palsy, accounting for 9 to 26% of cases of NBPP, is that of a total brachial plexus injury involving the C5-T1 roots; it is the most devastating injury to the brachial plexus with the least favorable outcomes.^{4,26,59,60} These newborns manifest flaccid, insensate paralysis of the entire arm and hand with pale or mottled skin due to vasomotor impairment; Horner syndrome (ptosis, myosis, enophthalmos, and anhydrosis) may or may not be seen. The final and exceedingly rare pattern of injury is that of Klumpke palsy, due to damage of the lower roots C8 and T1. The clinical features include a "claw hand" posture and Horner syndrome and are seen in fewer than 1% of obstetric palsies.⁵⁷

Neonatal injuries of the brachial plexus may be further subcategorized as supraclavicular, affecting the roots and/or trunks, or infraclavicular, involving plexus lesions distal to the level of the cords. The determination of the pre- or postganglionic nature of the level of injury is important for prognostic purposes.^{61,62} Preganglionic lesions are avulsions from the spinal cord that cause denervation weakness in all muscles supplied

by the injured root (motor cell bodies in the spinal cord), but nerve conduction (sensory cell bodies in the dorsal root ganglion) is intact. Damage to the nerves arising in proximity to the ganglion, including the phrenic (elevated hemidiaphragm), long thoracic (winged scapula), dorsal scapular (absence of rhomboid), suprascapular (rotator cuff), and thoracodorsal (latissimus dorsi) nerves, or the presence of Horner syndrome (preganglionic sympathetic fibers to the eye join the sympathetic chain from the T1 spinal nerve) resulting in mydriasis and ptosis suggests a significant preganglionic injury.⁶³ These cases do not recover motor function spontaneously. Postganglionic ruptures generally result in sensory conduction delay and the paralysis of target muscles innervated by the trunk level and beyond; such lesions have sufficient proximal and distal nerve components relative to the site of injury to be amenable to surgical repair and reconstruction.⁶⁴ A common pattern of injury is postganglionic rupture of the roots and trunks in the supraclavicular compartment (Erb palsy) and preganglionic avulsion in the infraclavicular compartment.^{59,65}

59.5 Natural History and Recovery Potential

As noted in the introduction, previous reports have documented that the majority of patients with NBPP have an overall favorable prognosis, showing that 70 to 95% had a complete spontaneous recovery with conservative management (physical therapy).^{6,55,66-68} Gordon et al found that 90% of patients showed improvement by 4 months of age, and Greenwald and others reported recovery within the first 3 months in 92% of patients.^{4,69} More recently, however, Hoeksma et al published a complete neurologic recovery rate of only 66% in a series of 56 patients, and Bager found severe impairment in 22% of 52 Swedish children with NBPP.^{8,70} We found at our own institution that 66% of 80 infants with NBPP achieved complete recovery, defined as antigravity movement in the biceps, triceps, and deltoid muscles by 4.5 months of age.⁹ In the cases of complete recovery, all patients achieved three-fifths strength in all three muscle groups by 5.5 months at the latest, and any permanent weakness was apparent by 6 months of age as two-fifths or lower strength in the biceps, triceps, or deltoid muscle. Narakas determined that satisfactory recovery in patients with total palsy was extremely unusual, and Al-Qattan et al found that none of 22 patients with Horner syndrome in their series achieved a positive outcome.^{54,71} Factors that portend a worse prognosis include total plexopathy and lower plexus injury, Horner syndrome, and multiple root avulsions.^{6,26,59,72} A systematic review by Pondaag et al in 2004 concluded that the most commonly reported high recovery rates were based on inadequate study methodologies limited by insufficient follow-up periods, unclear criteria for permanent injury, and lack of a final evaluation by a brachial plexus specialist.¹⁰ An evidence-based review focusing on prognosis following NBPP by Foad et al, published in 2009, reported that of 11 studies from 1966 through 2006 that met criteria for inclusion, only four achieved an Oxford evidence-based grading scale level of 1 or 2; they concluded that the quality of the literature on this subject is poor and that the rates of spontaneous recovery are significantly lower than those documented in early reports (even among

patients with upper trunk palsies, only 64% had a spontaneous recovery of biceps function at 3 months).⁷³

Despite the discordant data, several points remain clear. Most cases of NBPP are transient and show some improvement beginning as early as 2 weeks of age with supervised home therapy to support passive range of motion.⁷⁴ Infants who achieve partial antigravity strength in upper trunk-innervated muscles within the first 2 months are likely to progress to complete recovery over the next 2 years, whereas those who do not recover antigravity strength by 5 to 6 months after birth are unlikely to recover completely without surgical intervention.⁷⁵ Global shoulder function is increasingly impaired with longer duration of biceps muscle recovery, and these patients are likely to experience permanent, debilitating limitations of motion and strength as well as joint contractures.⁷⁶ Infants who demonstrate no signs of recovery and have a persistently flaccid arm at 2 months of age have a total palsy with an unfavorable long-term prognosis.^{26,41,67,77}

59.6 Patient Evaluation

59.6.1 Neurologic Examination

At our institution, patients in whom NBPP is diagnosed are evaluated as soon as possible after birth in a comprehensive multidisciplinary brachial plexus clinic comprised of a pediatric neurosurgeon, a pediatric neurologist, an orthopedic surgeon, physical and occupational therapists, a neuroradiologist, an electrophysiologist, and a nurse coordinator. A complete examination is performed, with the focus on a detailed obstetric and birth history, with the presence or absence of the aforementioned risk factors for NBPP noted. A careful assessment of passive range of motion of the involved arm, forearm, hand, and shoulder is made, often by simply observing spontaneous activity and coaxing the patient to reach for items with and without assistance. Numerous scales exist for evaluating motor strength, including the British Medical Research Council muscle movement scale, the Gilbert and Tassin muscle grading system, the Mallet scale, and the Hospital for Sick Children (Toronto) muscle grading system.^{78–81} We use the modified and simplified Medical Research Council scale (MRC 0–5) for all infants and, for patients older than 2 years who are able to cooperate, the Mallet scale in order to document functional changes in the shoulder and arm. In newborns, the presence or absence of a pinch response may provide useful information regarding sensory loss; evidence of self-mutilation of the fingers may be appreciated as well. Narakas classified the sensory responses of infants with NBPP into four groups.⁵⁴ Suspected associated injuries like rib, spine, clavicle, or humerus fractures or observed asymmetry of chest wall expansion should be clarified with inspiratory and expiratory plain radiographs. Fractures of the humerus and clavicle, the bones most commonly broken during delivery, can cause compression of the brachial plexus and a pseudoparalysis that mimics true NBPP.^{78,82,83} Other entities in

the differential diagnosis include congenital aplasia of brachial plexus nerve roots, congenital Varicella of the upper extremity, umbilical cord palsy, and intrauterine maladaptation palsy.

Typically, the inflammatory component of the birth trauma resolves over several days or weeks, and the true nature of the child's injury becomes more apparent. Many patients with palsies recover completely in this time frame, signifying a neurapraxic insult, whereas others improve from an entirely flaccid arm to a purely upper plexus palsy. Physical therapy in the form of passive range of motion exercises is initiated at home within the first month, and the patient returns to the clinic 4 weeks after birth. If the child still has a total palsy, particularly in the presence of Horner syndrome, the poor prognosis is explained to the parents and surgical intervention is discussed; numerous publications support microsurgical reconstruction in these infants by 3 months of age.^{59,64,79,84} If the patient exhibits evidence of improving hand function without shoulder or biceps recovery, physical therapy is continued, and he or she is seen on a monthly basis.⁸⁵ By 3 to 4 months of age, infants with antigravity strength or greater in the biceps, triceps, or deltoid muscle may be followed expectantly; children with less than antigravity strength in each of these muscles undergo neuroimaging and electrophysiologic studies in preparation for likely surgical intervention.⁹ If at 6 months of age the aforementioned muscles still have not recovered antigravity strength, brachial plexus exploration and repair are recommended. This practice pattern is based on our own prospective study of conservatively managed patients, in which we found that antigravity muscle strength at 3 months is prognostic for progression to a full recovery without an operation; similar strength testing at 6 months identifies those patients with less than antigravity strength who will not achieve a satisfactory outcome (antigravity strength) without surgery.⁸⁶ We believe this approach minimizes unnecessary surgical intervention in children destined to recover spontaneously yet avoids the development of irreversible joint contractures or permanent muscle atrophy in those patients who will ultimately benefit from microsurgical repair.

59.6.2 Other Tests

Ancillary studies often used in the evaluation of a patient with NBPP include plain radiography, electromyography (EMG) and nerve conduction studies, magnetic resonance (MR) imaging, and computed tomographic (CT) myelography. As mentioned, when phrenic nerve injury is a concern on examination, chest X-rays should be obtained to look for an elevated hemidiaphragm; when fractures of the ribs, clavicle, spine, or humerus are present, radiographs of the specific site of suspected injury should be obtained.

If a patient presents with NBPP without evidence of obstetric trauma and an intrauterine injury is considered, EMG is performed within a week of delivery to assess for denervation and to clarify the timing of the event.^{87,88} When surgical interven-

tion is proposed, EMG and nerve conduction studies are undertaken in some centers 3 months after birth. Details regarding the extent and distribution of the brachial plexus injury, as well as the expected pattern of recovery, may be collected; additionally, evidence of normal sensory conduction in the setting of severe motor weakness suggests a nerve root avulsion or preganglionic injury. Although EMG is standard in the work-up of adult brachial plexus injuries, its utility in the evaluation of NBPP is not as clear. Several studies have suggested that because denervation disappears early in newborn trauma and extensive collateral sprouting occurs rapidly to affected muscles, EMG may not accurately portray the severity of the clinical condition.⁸⁹ We have not found EMG to be particularly helpful in our own practice.

When the decision is made to proceed with brachial plexus exploration, we use T1- and T2-weighted fast spin-echo cervical MR imaging sequences to look for pseudomeningoceles as a marker for nerve root avulsion, as well as any sign of spinal cord injury.^{90,91} It is worth noting, however, that 15% of pseudomeningoceles are not associated with complete nerve root avulsion, and 20% of surgically diagnosed avulsed roots may not be associated with a pseudomeningocele.^{49,92} A retrospective review by Smith et al in 2008 demonstrated in a small group of infants with birth-related brachial plexus injuries the ability of MR neurography to aid in the anatomical localization and characterization of nerve swelling, neuromas, and denervation changes.⁹³ CT myelography is an invasive alternative to MR imaging that provides a better delineation of the nerve roots and intervertebral foramina but requires general anesthesia, lumbar puncture, intrathecal contrast, and exposure to radiation.

59.7 Timing of Surgery

The primary clinical dilemma is to determine if an infant with NBPP warrants surgical exploration and reconstruction, and the absence of motor recovery is the main indication for operative intervention. Because these patients have varying degrees of nerve pathology (Sunderland II through IV) and their neuromuscular recovery following conservative management versus that after microsurgical intervention have not yet been compared in a prospective or randomized controlled manner, the timing of surgical treatment remains controversial.⁹⁴ As early as 1917, Wyeth and Sharpe advocated surgery if there were no signs of motor recovery 3 months after birth.⁷⁷ Many authors cite Gilbert and Tassin's classic study of 44 children with NBPP in whom recovery of the biceps muscle at 3 months of age served as the indicator for expected spontaneous recovery (shoulder function was better in infants who showed biceps and deltoid recovery before 3 months) and recommend surgical exploration at 3 months if sufficient improvement has not occurred.⁸⁰ Laurent et al espoused close monitoring of the triceps and deltoid muscles, in addition to the biceps, to determine microsurgical intervention.⁵⁹ Chuang et al proposed that an aggressive approach (exploration at 3 months) is indicated for total palsy but only relatively so for lesions of the upper plexus.⁹⁵ We found in our own series that patients who continued with

less than antigravity biceps strength by 6 months of age had unsatisfactory outcomes with nonsurgical management.⁹ Terzis and Papakonstantinou argued for operative intervention at 4 to 6 weeks in patients with severe global injuries and at 3 months in children with isolated C5–C6 deficits and absence of antigravity biceps or deltoid recovery.²⁵ Clarke and Curtis, on the other hand, recommended employing the “cookie test” to evaluate isolated elbow flexion recovery at 9 months of age as a measure of prognosis and to guide surgical treatment.⁷⁸

59.8 Surgical Treatment

59.8.1 Anesthesia and Exposure

Before the operation, we make a concerted effort to counsel the parents regarding expectations and emphasize that the goal of surgery is to improve the functional capabilities of the arm, that it may never be completely normal, and that recognizable benefits may not appear for up to 6 months.

Surgery is performed under general anesthesia with a short-acting neuromuscular agent to permit intraoperative electrical stimulation.³⁰ Following induction, the patient is positioned supine with a gel shoulder roll placed to elevate the clavicular region, and the head is rotated contralaterally. The entire neck, chest, and affected upper extremity and both lower limbs are prepared in a sterile manner to allow visual inspection of the muscles of the affected arm during surgery and to accommodate the potential need for bilateral sural nerve graft harvesting; this last point has been modified recently at our own institution as we have started using a peripheral nerve allograft in lieu of sural nerve autografts (Avance; AxoGen, Alachua, FL) in order to spare the patient a second (or third) surgical site. For an Erb or upper trunk palsy, a standard supraclavicular approach is used, whereas treatment of the lower plexus requires an infraclavicular exposure. The incision for the former begins two fingerbreadths beneath the mastoid tip and follows the posterior border of the sternocleidomastoid muscle to the midpoint of the clavicle; if a combined approach is indicated, the incision is extended laterally along the superior border of the clavicle to the deltopectoral groove and curved inferiorly to the anterior axillary fold. The entire operation is done under microscopic visualization.

Once the incision is made through the skin and platysma muscle for the supraclavicular approach, the flaps are raised, and a layer of fibrofatty tissue overlying the brachial plexus posterior to the sternocleidomastoid muscle is elevated with sharp dissection. The omohyoid muscle is divided, and the transverse cervical vessels are retracted or cauterized. Dissection continues down to the clavicle, with subsequent division of the subclavius muscle and clavicular periosteum. Although some authors routinely perform a clavicular osteotomy to improve exposure for combined approaches, others connect the supra- and infraclavicular plexus elements through subclavicular blunt dissection; if necessary, the clavicular portion of the pectoralis major muscle may be dissected from the clavicle, with preservation of the pectoral nerve, in order to expose the cords of the brachial plexus.⁹⁶

The first goal is to reveal the C5 and C6 nerve roots and upper trunk, which requires identification of both the phrenic nerve along the anterior scalene muscle and the spinal accessory nerve arising from the C4 root; the latter may be seen at the posterior junction of the upper and middle thirds of the sternocleidomastoid muscle. Direct electrical stimulation and observation of responses are used throughout the dissection and aid in the labeling of these nerves. The upper trunk neuroma is likely to be readily apparent, and the C5 root is identified by tracing the most superficial portion of the upper trunk toward the neural foramen. The anterior scalene muscle is then divided and partially resected to provide access to the C6–T1 nerve roots; care must be taken when the T1 root is exposed, given its proximity to the pleura and subclavian vessels. Soft Silastic (Dow Corning, Midland, MI) vessel loops are used to designate and retract the roots, while the three trunks are identified close to the clavicle and freed from surrounding fibrotic tissue. The dorsal scapular and suprascapular nerves will be located arising from the C5 root and upper trunk, respectively; the long thoracic nerve will often be found under the upper trunk above the middle scalene muscle. Infraclavicular exposure is achieved by dissecting along the deltopectoral groove, with subsequent division of the pectoralis major at its insertion into the humerus and at the midpoint of the pectoralis minor; the cephalic vein is preserved, and marking sutures are used in the pectoralis major to facilitate closure. At this point, the cords of the brachial plexus as well as the median, ulnar, musculocutaneous, and axillary nerves may be identified.

Traditionally, we have harvested autologous sural nerve grafts through bilateral open posterior lower leg stepladder incisions; endoscopic harvest of the sural nerves has also been described.⁹⁷ Because the sensory sural nerves are smaller than the mixed nerves of the brachial plexus, multiple segments of sural nerve are needed following neuroma resection to create an adequate graft spanning the distance from nerve root to trunk. This requires a second or third incision, increases the risk for wound infection, and may cause postoperative pain or paresthesias. Recently, we have instead used a decellularized and sterile extracellular matrix processed from donor human peripheral nerve tissue called Avance. Alternative donor sites include nerves in areas of the patient's own plexus where reinnervation is unlikely to occur, including the medial cutaneous nerve of the forearm.

59.8.2 Resection of Neuromas

Surgical options for the treatment of neonatal brachial plexus palsy include neurolysis, complete or partial resection of the neuroma, and repair by nerve grafting with or without intra- and/or extra-plexus nerve transfers.⁹⁸ External neurolysis alone is employed only when the neural elements show evidence of mild traction injury without disruption of the perineurial sheath; the resection of conducting neuromas in continuity has been shown to have better results than neurolysis alone.⁹⁹ Nevertheless, controversy exists regarding the optimal intraoperative management of neuromas, particularly in light of the fact that the use of nerve action potential measurements during surgery as a prognostic tool has not been validated in the pedia-

tric population.^{100,101} Some authors resect all neuromas unless distinct fascicular architecture is observed.^{26,29,41,67} Laurent and colleagues depend on the intraoperative assessment of compound muscle action potentials (CMAPs) across a neuroma to determine whether to perform neurolysis or neuroma resection and nerve grafting; a drop in the CMAP of more than 50% indicates resection, and a drop of less than 50% results in neurolysis.^{58,59,102} We combine a semiquantitative evaluation of muscle contraction in response to electrical stimulation of the nerve root proximal to the neuroma with intraoperative inspection of the neuroma, awareness of the preoperative muscle strength, and knowledge of the MR imaging findings to arrive at a decision. Generally, if the root or trunk is ruptured and electrical stimulation of up to 10 milliamperes generates no or minimal muscle contraction, the neuroma is resected. If there is evidence of nerve root avulsion and weak conduction through the remaining nerve root, then the nerve root sheath is divided. If the brachial plexus is in continuity but elicited muscle contraction is poor, the neuroma is resected. If the brachial plexus is in continuity and strong muscle contraction is observed following electrical stimulation of the proximal nerve root and the neuromas are not extensive, no resection is undertaken.

59.8.3 Repair Procedures

The primary objective of surgery for Erb or upper trunk palsy is to restore shoulder and biceps muscle function through a variety of grafting and neurotization procedures. These include using the stumps of the C5 and/or C6 roots, the C7 nerve root, or the spinal accessory nerve for grafting to all or part of the upper trunk, suprascapular nerve, and axillary nerve arising from the posterior cord. For total plexus injury, multiple nerve grafts must be employed. If several nerve root stumps are identified, these are divided and used for grafting all trunks and cords of the brachial plexus. If only a single nerve root stump is accessible, it is grafted to the musculocutaneous nerve. All nerve grafts should be prepared 10 to 15% longer than the measured defect length and combined to match the diameter of the host nerves. Neuroorrhaphy is performed with 9–0 Prolene (Ethicon, Somerville, NJ) epineurial sutures combined with fibrin glue.

Nerve root avulsions require neurotization. Historically, this has meant nerve crossover or transfer between an uninjured neighboring donor nerve and a distal segment of a nonfunctioning nerve directly or with grafts. Nerve transfers involve motor-to-motor neural connections and may be used primarily or in late cases to augment function in the setting of partial neurologic recovery.⁶³ Spinal accessory, phrenic, intercostal, medial pectoral, thoracodorsal, long thoracic, and subscapular nerves have all been used for neurotization. When a transfer of the spinal accessory nerve to the suprascapular nerve is used to reinnervate the infra- and suprascapular muscles, care must be taken to section the nerve distal to the first branch to the trapezius muscle in order to avoid a significant motor deficit.^{22,103} This can be combined with a transfer of the long head of the triceps motor branch of the radial nerve to the anterior portion of the axillary nerve for improved shoulder abduction.^{10,104–106} Al-Qattan and others have employed the technique described by Oberlin et al for transferring the fascicles of the ulnar nerve that

supply the flexor carpi ulnaris to the motor branches of the biceps in patients with good recovery of shoulder function but little or no elbow flexion; more recently, transfer of the motor fibers of the median nerve and medial pectoral nerve has also been described in such children with good success.¹⁰⁷⁻¹¹¹ We perform the transfer only in the setting of a secondary operation, either when the primary neurolysis/grafting did not result in adequate biceps function (as above) or when the primary exploration revealed such severely traumatized roots/trunks that grafting was impossible (one patient who returned at a later date for multiple transfers). We do think, however, that the Oberlin transfer could be considered at the primary operation for a patient who achieved spontaneous recovery of shoulder function without satisfactory recovery of biceps function by the 6-month time point. The phrenic nerve transfer has also proved safe and effective in adults with normal diaphragmatic function but is not recommended in infants in light of their immature respiratory system and greater risk for fatal pulmonary complications. Additionally, the long-term efficacy of neurotization with the long thoracic, thoracodorsal, subscapular, and pectoral nerves in babies is unknown.

Wound closure is performed in layers, including reinsertion of the pectoralis major muscle (if sectioned) and the platysma muscle, in a routine manner. The shoulder is maintained in adduction over the trunk with an elastic bandage and sling, and a soft collar is applied to the neck.

59.8.4 Complications

Risks of the surgery include loss of preoperative muscle strength, injury to the phrenic nerve with diaphragmatic paralysis, cerebrospinal fluid leak, pneumothorax, thoracic duct injury (left-sided approach only), injury to the carotid and subclavian arteries or to the jugular and subclavian veins, pseudoarthrosis of the clavicle in the setting of clavicular osteotomy, and wound infection. Rarely, a wound hematoma or airway edema may result in respiratory compromise, and the patient must be monitored closely for evidence of airway insufficiency and swallowing dysfunction.

59.8.5 Postoperative Care

Most of our patients are discharged on postoperative day 2 or 3. The affected arm is immobilized in a sling for 3 weeks, at which point physical therapy is initiated to prevent joint stiffness and contractures. The patient is seen every 3 months in the clinic, and pain control is generally not a challenge when acetaminophen or ibuprofen is used. Other authors advocate the prolonged use of a cast placed in the operating room with subsequent use of a sling for several months before the initiation of physical therapy.

59.8.6 Outcomes

The results of surgery depend not only on the severity of the injury but also on the extent of root avulsions. Recovery typically begins within 2 to 10 months after surgical intervention and may continue until the patient is 5 years old. A 1995 report by

Gilbert et al of 178 cases treated with nerve reconstruction showed excellent results for repairs in children who had Erb palsy with regard to shoulder and elbow function; in 54 children with global palsy, reinnervation of the lower trunk achieved useful finger flexion in 75% of cases.¹¹² Multiple authors have demonstrated that neurologic improvement occurs in 75 to 95% of patients undergoing surgical reconstruction, with most achieving antigravity strength in the shoulder and/or elbow.^{29,60,79,102,113} Because the goal of surgery is not only to restore function but also to prevent permanent changes in the denervated muscle that may create long-term orthopedic deformities, the objectives include the following: stabilization of the shoulder through reinnervation of the supraspinatus and deltoid muscles, restoration of elbow flexion with reactivation of the biceps, and improvement of median nerve sensory function in cases of lower or total palsies in preparation for future secondary reconstruction procedures.¹¹⁴ Boome and Kaye published results including antigravity strength in 95% of the deltoid and 80% of the biceps muscles in patients following surgery; Laurent et al found that 85 to 95% of patients recovered antigravity strength above the elbow and noted a 50 to 70% recovery rate distal to the elbow.^{41,58,102} In our own series, those patients undergoing exploration and repair for upper plexus lesions achieved better results than those having surgery for lower plexus injuries.⁸⁶

59.8.7 Secondary Reconstruction

Up to 35% of infants and children with chronic NBPP commonly experience specific secondary deformities at each joint due to the unopposed contraction of innervated muscle groups, the presence of joint contractures, and the occurrence of abnormal stressors affecting the upper limbs.^{8,10} A review by Zancolli et al reported rates of secondary deformities of 72% for internal rotation contracture of the shoulder, 62% for flexion contracture of the elbow, 69% for supination contracture of the forearm, and 27% for ulnar deviation of the wrist and varying types of finger paralysis.¹¹⁵ Secondary reconstructions are often performed when such patients attain a rehabilitation plateau. The most common presentation is internal rotation contracture at the shoulder due to muscular imbalance between the active internal rotators and the paralyzed external rotators in patients with upper plexus injuries. Management by orthopedic surgeons includes serial clinical and radiologic assessments, muscle releases and muscle or tendon transfers, rotational osteotomies, and later shoulder arthrodesis. Grossman et al published their experience in infants aged 11 to 29 months with brachial plexus birth injuries. They used a late combined reconstruction of both the upper brachial plexus via end-to-side neuroorrhaphies and the shoulder via subscapularis slides with or without glenohumeral joint reduction and capsulorrhaphies; their findings of improvement in all patients of at least two grades on a modified Gilbert scale suggest that some children presenting late with persistent neurologic deficits and concomitant shoulder deformities may benefit from this type of simultaneous treatment.¹¹⁶ Weakness of elbow flexion may be addressed with a bipolar latissimus dorsi pedicle muscle

transfer or a functional muscle transfer performed in two stages. Extension deficit or elbow flexion contracture is also common and may be due to cross-innervation and muscle imbalance (stronger biceps than triceps) following spontaneous recovery from Erb palsy; because this is frequently observed in association with internal rotation contracture of the shoulder, surgical treatment of the shoulder deformity will typically improve the elbow contracture.^{117,118} Additionally, joint splinting, muscle or tendon release, and extension osteotomy of the distal humerus may be necessary. The usual birth palsy forearm deformity of slight pronation does not require intervention because the hand is in a functional position; the supination posture seen in patients with global palsy, however, may require biceps tendon rerouting, interosseous membrane release, and rotational osteotomy of the radius or proximal radioulnar arthrodesis.^{119,120} Finally, the lack of wrist extension in patients with upper plexus palsies is frequently reconstructed with a flexor carpi ulnaris or radialialis muscle transfer; the wrist instability observed in some patients with total paralysis is treated with arthrodesis after skeletal maturity is achieved.¹²¹

59.9 Conclusion

Despite increased awareness of the etiology and risk factors and improved obstetric techniques, the incidence of birth-related brachial plexus palsy has not declined in recent years. Although many neonates with birth palsy attain spontaneous recovery within weeks of the occurrence, others fail to improve with conservative therapy. We favor a process of close and frequent follow-up in our multidisciplinary clinic, with a recommendation for surgery earlier than 3 months in cases of total plexus palsy. We have demonstrated that the motor examination at 3 months of age is predictive of a favorable outcome if antigravity strength of the deltoid, biceps, and triceps muscles is present; such patients are managed with physical therapy alone. Similarly, we have shown that strength testing at 6 months of age is predictive of a poor functional outcome if antigravity strength in the aforementioned muscle groups is not achieved; surgical intervention is recommended in these cases. Patient evaluation includes a detailed neurologic examination, chest radiography, EMG, and MR imaging of the cervical spine and brachial plexus. The surgical approach is tailored to each patient's specific injuries, and repair strategies include neurolysis, neuroma resection and grafting, and nerve transfers; intraoperative electrophysiology may aid in the determination of the ideal reconstructive technique. We have recently used a decellularized peripheral nerve allograft in place of a sural nerve autograft with reduced operating time, a closer size match between graft and brachial plexus neural elements, and improved postoperative pain control due to the absence of leg incisions. The outcomes of primary brachial plexus reconstructions have been shown to be positive, with most patients making functional gains, particularly in the setting of upper trunk injuries. For those patients with chronic joint deformities due to unopposed muscle activity and contractures, secondary orthopedic surgery in the form of tendon releases, muscle transfers, osteotomies, or arthrodesis procedures may be necessary.

Pearls

- Despite the fact that most birth-related brachial plexus injuries are mild and improve after conservative management, the rates of spontaneous complete recovery are not as high as once believed.
- Although controversy exists regarding the optimal timing for surgical intervention, close follow-up and careful patient selection, combined with the use of microsurgical techniques, have achieved excellent functional outcomes in patients with pediatric brachial plexus palsies.
- Early surgery (within 3 months) should be considered for patients with global palsy, and a lack of antigravity strength in the deltoid, biceps, and triceps muscles at 6 months of age is an indication for primary operative reconstruction.
- A variety of repair options exist, including nerve grafting and neurotization, and the combination of detailed anatomical knowledge, MR imaging findings, and intraoperative electrophysiology allows the surgeon to tailor the repair to each patient's needs.
- The use of biodegradable nerve guidance channels and decellularized human donor peripheral nerve allografts offers an alternative to autologous sural nerve grafts; a randomized controlled trial comparing these entities is likely indicated.
- Parent counseling is critical throughout the process regarding expectations; the goal of primary surgery is to improve the functional capabilities of the arm, recognizable benefits may not appear for up to 6 months, and outcome is determined only after several years of recovery.
- Patients should be seen in a multidisciplinary brachial plexus clinic because many will manifest secondary sequelae of birth-related brachial plexus injuries, such as joint contractures, and will benefit from early orthopedic evaluation and intervention.

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60 Principles of Pediatric Spinal Column Trauma

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The unique anatomical characteristics of the developing spinal column change dramatically from infancy through childhood and into adolescence. These anatomical characteristics directly influence spinal biomechanics, which subsequently influence the response of the pediatric spine to physiologic and pathologic forces. Although prevention is the most effective means to combat pediatric spinal column injuries, a thorough understanding of these relationships is necessary to provide optimal care to children following vertebral column trauma.

This chapter addresses the underlying principles of pediatric spinal column trauma without focusing on specific injury types or the neurologic outcomes of injury. Specifically, the epidemiology, developmental anatomy, biomechanics, initial management, and diagnostic imaging pertaining to traumatic injuries of the immature spinal column are discussed. Additionally, information on the general principles of external and internal immobilization in the treatment of these injuries is included. Specific types of traumatic injury affecting the pediatric spinal column—including injury description, clinical presentation, radiographic diagnosis, and appropriate treatment—are discussed at length in the next chapter.

60.1 Epidemiology

The epidemiology of pediatric spinal column trauma is influenced heavily by patient age, which is closely associated with the incidence of injury, etiology and mechanism of injury, male-to-female ratio of injured patients, the vertebral level most likely to be injured, and the injury pattern.

60.1.1 Frequency

Occurring less frequently than in adults, pediatric spine injuries account for only 5 to 7% of all spine injuries that present to major medical centers.¹ The incidence of spine injury in children less than 19 years of age in the United States is approximately 20 injuries per million per year.¹ There is a seasonal variation in the incidence of pediatric spinal column trauma in North America, with a peak in the summer months from June to September and an additional increase in incidence during the winter holidays at the end of December and beginning of January.²

60.1.2 Etiology

The etiology of traumatic injuries to the pediatric spinal column varies depending on the age of the patient. Overall, in North America, motor vehicle accidents comprise the single most common cause of injury. In younger children (birth to 9 years of age), falls and pedestrian-versus-vehicle accidents account for as many as 75% of injuries.^{1,3,4} In children 10 to 14 years of age, motor vehicle accidents become more prevalent and account for 40% of cases, with falls and pedestrian accidents decreasing in frequency. In late adolescence (ages 15 to 17 years), motor vehicle accidents predominate as the leading cause of spinal column injury, accounting for more than 70% of cases in some

series. Sports-related injuries also become more frequent, and sports are the second most common etiology in this age group.^{1,3-6}

60.1.3 Gender

The male-to-female ratio of children with spinal column injuries varies with age, in concordance with the shift in etiology. In the youngest age group (birth to 9 years of age), the male-to-female ratio (1.1 to 1.3:1) is the smallest because pedestrian accidents tend to affect both genders equally, whereas boys are slightly more susceptible to falls.^{1,3,6} The ratio becomes significantly higher as one approaches the 15- to 17-year-old group (2.3 to 2.5:1), presumably because of a propensity of males to participate more frequently in aggressive sports and reckless driving.^{1,3,6}

60.1.4 Level of Injury

The vertebral level of injury in pediatric patients with spinal column trauma is strongly correlated with age, as predicted by the biomechanics of the immature spine. Numerous studies have demonstrated that the majority of spinal cord and vertebral column injuries occur in the cervical region within this age group.⁷ Two large series of pediatric spinal column injuries reported that the injuries were located in the cervical spine in almost two-thirds of patients (61%), followed by lumbar (14%), thoracolumbar (14%), and thoracic locations (11%).^{3,7} In particular, younger children are more likely to have upper cervical spine injuries, and as patient age increases, the most frequently injured level moves progressively caudal. Upper cervical and craniovertebral junction (CVJ) injuries are two to three times as frequent in children less than 3 years old than in older children and adults.^{3,6,8} In contrast to upper cervical injuries, whose frequency is largely influenced by age, lower cervical and thoracic injuries occur with approximately equal frequencies in both younger (birth to 9 years) and older (10 to 17 years) children because maturation of the spine at these regions occurs much more gradually than at the CVJ.^{6,9} Thoracolumbar and lumbar injuries are primarily lesions of adolescence. Of important consideration in pediatric spinal column trauma is the high incidence of multilevel contiguous (26 to 34%) and noncontiguous (6 to 16%) injuries.^{1,3,10,11} Subaxial cervical spine injuries involving multiple levels are more common in children 8 years of age or older than in younger children.¹² This highlights the need to survey the entire vertebral column in every child who presents with a spinal column injury.

60.1.5 Injury Pattern

Pediatric spinal column trauma is typically classified according to radiographic findings on plain X-ray and computed tomography (CT). Magnetic resonance (MR) imaging is generally less useful in the initial classification of injury types but has utility in the assessment of stability through a more detailed examination

of the associated soft tissues. Based only on skeletal information from imaging with X-rays and CT, four injury patterns are seen in children with spinal column trauma: (1) fracture with subluxation, (2) fracture without subluxation, (3) subluxation without fracture (purely ligamentous injury), and (4) spinal cord injury without radiographic abnormality (SCIWORA).¹³ Although an oversimplification, there is a rough correlation with the degree of instability inherent in this classification: fractures with subluxation are generally unstable; fractures without subluxation may or may not be unstable, depending on the amount of associated ligamentous injury; subluxation without fracture is by definition unstable, although the instability may not manifest immediately but instead later, as a delayed or progressive kyphotic deformity. SCIWORA is a very rare form of radiographically occult instability that is not demonstrable on imaging with conventional X-rays or CT. In the vast majority of cases, however, radiographic abnormalities are seen on MR imaging. Immobilization measures should be undertaken to prevent possible recurrent, progressive, or catastrophic injury.

Age profoundly affects the injury pattern within the pediatric population. In general, younger children (0 to 9 years) are most likely to have a purely ligamentous injury or SCIWORA, whereas older children (10 to 17 years) are more likely to have fractures with or without associated subluxation.^{1,3,14} In children with cervical spine injuries, the incidence of fracture is approximately 20 to 25% in the 0- to 8-year range versus 70 to 80% in children older than 13 years.¹⁵ Despite these numbers, it is important to note that although vertebral column fractures are less frequent in younger children, they are not uncommon; in some series, the incidence of fracture in children 0 to 9 years old with spinal column trauma has been reported to be as high as 50%.^{1,3}

In addition to the influence of age on the pattern of spinal column injury, there is a significantly higher incidence of neurologic injury in younger versus older children. The degree of neurologic compromise has been shown to correlate with the presence of subluxation. As such, children having fractures without subluxation tend to have fewer neurologic injuries (20 to 25%) than those with fracture and subluxation or subluxation without fracture (purely ligamentous injury) (>50%).³ Furthermore, among children with spinal cord injury (SCI), younger children are more likely to experience severe SCI.^{1,3} In most case series of pediatric spine trauma, the numbers of patients who are neurologically intact and those with SCI are approximately equal.^{1,3-6}

60.2 Embryology

Embryogenesis of the spinal column occurs in six separate but overlapping phases: (1) gastrulation, (2) condensation, (3) reorganization, (4) membranous proliferation, (5) chondrification, and (6) ossification. Congenital malformations are generally the result of errors during one of the first five phases, whereas the ossification phase is the most important with regard to the response of the vertebral column to trauma and its subsequent management.

Gastrulation occurs during the second week of embryogenesis, when the embryo is converted from a two-layered to a three-layered structure containing ectoderm, mesoderm, and

endoderm. This process begins with formation of the primitive streak at the caudal end of the embryo. As the primitive streak subsequently regresses, mesodermal cells from the Hensen node ingress through a primitive pit to form the midline notochord.^{16,17} The elongating notochord is flanked on each side by newly developed somitic mesoderm; together, these tissues ultimately form the axial skeleton (the intervertebral disks and vertebrae, respectively).

Once in final position, the somitic mesoderm aggregates into discrete, bilaterally paired blocks of tissue, called somites, in a process termed condensation. Both the notochord and somite pairs develop and mature in a rostral-to-caudal direction. The maximum number of somites in the human embryo is generally reported to be 42 to 44, although no more than 38 or 39 are required for formation of the axial skeleton.¹⁸

Reorganization involves the development of two segments within each somite: a ventral sclerotome, which contributes to the axial skeleton, and a dorsal dermomyotome, which becomes the dermis and subcutaneous tissues of the back and the dorsal trunk musculature.

The membranous phase of spinal column development begins during the fifth week of embryogenesis. Sclerotomal cells from each somite pair migrate toward the midline and surround the notochord ventrally and the neural tube dorsally. The vertebral centrum is formed by the merging of these cells on either side of the notochord and becomes visible in human embryos shortly thereafter. Craniocaudal polarity begins during somite formation and is restricted to the sclerotomal portion of the somite.¹⁹ The dorsal arch of each vertebra appears to be exclusively derived from the caudal, more densely packed, half of the sclerotome. Most evidence tends to support the concept of resegmentation, in which each somite pair directly contributes to the formation of two adjacent vertebral centra.^{20,21} This accounts for the observation that each spinal nerve passes caudal to its corresponding pedicle.

Chondrification centers appear within the sclerotomes during the sixth embryonic week. The annulus of the intervertebral disk is produced from the condensation of cells from perinotochordal tissues, while physaliphorous cells of the notochord form the central nucleus pulposus. The anterior longitudinal ligament and posterior longitudinal ligament also form during chondrification.

The ossification phase begins in the eighth week of embryogenesis and continues until adolescence.²² It is the most relevant phase of spinal embryogenesis with regard to the ability of the pediatric spine to withstand traumatic forces. The total number of ossification centers that form within each vertebral segment is still the subject of debate; however, most authors argue for three primary ossification centers: one for the vertebral centrum and one on each side for the dorsal vertebral arch. The ossification centers on each side of the dorsal arch subsequently form three progressively independent zones of ossification: one each for the pedicles, lamina, and transverse processes. The junction of the ventral and paired posterior ossification centers occurs at the neurocentral joint. Importantly, the neurocentral joint lies within the vertebral body, not at the junction of the pedicle with the body. Thus, the centrum, combined with the more ventral portions of the dorsal ossification centers, gives rise to the vertebral body. The terms *centrum* and *vertebral body* are therefore not strictly synonymous.

Cartilaginous zones subsequently appear cranial and caudal to the ventral ossification center at the cartilaginous end plates. The ring apophysis, a C-shaped structure, forms at the periphery of the cartilaginous end plates, between the developing intervertebral disk and the expanding ossification center of the vertebral centrum. By 11 to 14 years of age, foci of ossification appear within the ring apophysis and become confluent by 15 years of age, forming the radiographic ring. The ring apophysis fuses with the vertebral centrum during middle to late adolescence. This is particularly relevant since during childhood and adolescence the unfused ring apophyses may fracture in response to trauma, which can simulate a herniated disk with nerve root impingement, but is less likely to respond to conservative therapy.²³

The CVJ develops from the four occipital sclerotomes (somites 1 through 4) and the first and second cervical sclerotomes (somites 5 and 6). The occipital bone, clivus, and occipital condyles form from the four occipital sclerotomes (somites 1 through 4), with the condyles, paracondylar processes, and ring of the foramen magnum arising from the fourth occipital sclerotome (somite 4). The atlantoaxial complex forms from the fourth occipital sclerotome (somite 4) and the first and second cervical sclerotomes (somites 5 and 6).

Chondrification of the CVJ begins by embryonic day 45, and the cartilaginous anterior arch of C1 appears by day 50 to 53.²³ The anterior arch of the atlas is not ossified in 80% of newborns, and ossification is completed between 6 and 24 months postnatally. A synchondrosis is occasionally present in the anterior arch midline and should not be confused with a fracture.

The odontoid process separates from the atlas between the sixth and seventh weeks of embryogenesis.²⁴ Fusion of the odontoid process to the axis body at the dentocentral synchondrosis begins at about 4 years of age and is completed by 8 years; however, it has been known to remain visible on lateral radiographs in 50% of children up to 11 years old.²⁵ A common radiographic misinterpretation is that of the dentocentral synchondrosis as a type II odontoid fracture; however, the location of the synchondrosis is actually below the anatomical base of the odontoid. Injury to this area in young children is usually not technically a fracture, but rather epiphysiolysis of the dentocentral synchondrosis. The apical ossification center is generally visible by age 3 and fuses to the rest of the odontoid process by age 12. The apical synchondrosis can often be misinterpreted as a type I odontoid fracture. Failure of ossification of the apical synchondrosis is termed *ossiculum terminale persistens* (or *os avis*) and is not considered to be a pathologic condition.

60.3 Biomechanics

60.3.1 General Principles

The developing spine has several unique anatomical and physiologic properties that result in biomechanics that are significantly different from those of the mature adult spine. The main biomechanical difference between the pediatric and adult spine is that the developing spine is inherently more malleable to physiologic and pathologic forces and thus can withstand considerable movement between vertebral segments without damage, but at the cost of providing less protection to the underlying spinal cord.

The developing spine undergoes a biomechanical maturation at approximately 8 to 9 years of age, after which it more closely resembles that of adults.^{14,25–27} Evidence indicates that this transition takes place more abruptly in the upper cervical spine than in the lower cervical or thoracolumbar spine.^{3,6,27} The single most important concept in spinal biomechanics is that of stability. Instability has been defined by White and Panjabi as “loss of the ability of the spine under physiologic loads to maintain its pattern of displacement so that there is no initial or additional neurological deficit, no major deformity, and no incapacitating pain.”²⁸ Current models to predict injury have important limitations, particularly with respect to the pediatric spinal column. Few studies have directly investigated the biomechanics of the developing spine; therefore, many assumptions regarding its biomechanics are extrapolations from adult clinical and laboratory data, and these are viewed as particularly inaccurate with regard to the CVJ.

Despite these limitations, several general biomechanical premises and predictions relating to the developing pediatric spine have been suggested.²⁹ First, the malleability of the developing spinal column is increased by its more elastic ligaments, so that it is less likely to sustain fractures and ligamentous rupture when subjected to extrinsic forces but more likely to result in SCIWORA. Second, because it is more malleable, the pediatric spine undergoes more intervertebral displacement in response to extrinsic forces, affording less protection to the spinal cord, making SCI possible in the absence of fracture or subluxation. Third, the most unstable region of the developing spinal column is the upper cervical spine. Trauma to this region should result in fewer fractures but more severe SCI in young children than in older children and adults. Finally, the pattern of SCI in older children (more than 8 years old) should closely resemble the patterns seen in adults, with lower cervical injuries being more common.

60.3.2 Craniovertebral Junction

The occipitoatlantoaxial (O–C2) complex functions as the biomechanical unit of the CVJ. Interacting together as a single unit, the occipitoatlantal (O–C1) and atlantoaxial (C1–C2) joints control movement of the head in relation to the subaxial spine. The atlas (C1) functions as a biconcave washer wedged between the occipital condyles and the superior articulating facets of the axis (C2). The articulation between the occipital condyles and C1 (O–C1) is cup-shaped in the sagittal plane and tilted medially in the coronal plane. This orientation allows up to 20 degrees of flexion–extension and 8 degrees of lateral bending at the joint.²⁸ Further extension at O–C1 is limited by contact of the posterior arch of the atlas with the opisthion at the base of the skull.³⁰ Lateral bending of more than 8 degrees in either direction is inhibited by the contralateral O–C1 joint capsule. The oblique orientation of the O–C1 articulation precludes all but 4 degrees of rotation to either side at this joint.^{31,32}

Although essentially no lateral bending occurs at C1–2, the articulation between the lateral masses of C1 and C2 is biconcave in the sagittal plane and tilted laterally in the coronal plane, allowing a large degree of axial rotation centered on the odontoid process.^{28,33} Rotation at C1–2 ranges from 32.2 to 47 degrees to one side and accounts for up to 60% of the

rotation of the entire cervical spine.^{34–36} The first 20 to 30 degrees of head rotation occurs predominantly at the C1–2 joint, during which C1 moves independently of C2. As head rotation passes beyond 30 degrees, the C1–2 joint capsules and alar ligaments begin to reach the limit of their ability to stretch and C2 begins to follow C1 in rotation, but C1 continues to rotate faster than C2.^{31,34} The maximal degree of rotation between C1 and C2 is reached at approximately 47 degrees. Subsequent head turning is then accomplished by rotation of the subaxial spine. It is important to note that axial rotation is coupled to other motions within the CVJ. Maximal rotation is associated with 1.7 to 4.9 degrees and 3 degrees of lateral bending to the opposite side at O–C1 and C1–2, respectively.³⁶ Rotation is additionally coupled to extension, with up to 13 degrees of extension at O–C1 and 6 degrees at C1–2. Finally, because of the biconvex articulation between C1 and C2, downward translation occurs at this joint with rotation. Before spinal maturation, there is exaggerated motion at the articulation between the anterior arch of the atlas and the odontoid process. Flexion–extension of up to 20 degrees can occur at C1–2 because of physiologic overriding of the anterior arch of C1 along the dorsally curved odontoid process, particularly in very young children (younger than 3 years old), in whom the apex of the odontoid process is not yet ossified. The normal atlantodental interval (ADI) is less than 5 mm in children before spinal maturation (less than 8 years), compared with a normal value of less than 3 mm in adults. Twenty percent of normal children younger than 8 years have an ADI between 3 and 5 mm.²⁵

Stability of the CVJ is provided by several major elements: the cup-shaped O–C1 articulation and its associated capsular ligaments, the tectorial membrane, the alar ligaments, the odontoid process, and the transverse portion of the cruciate ligament.^{37–39} The transverse ligament is the thick horizontal portion of the cruciate ligament and is the primary constraint to posterior translation of the odontoid into the spinal canal. The tectorial membrane is a continuation of the posterior longitudinal ligament and functions to hold the body of C2 firmly to the clivus and anterior rim of the foramen magnum. Flexion at the CVJ is limited initially by contact between the basion and odontoid process. The tectorial membrane limits additional flexion as the basion slides forward and downward over the odontoid tip. Extension at the CVJ is also limited by the tectorial membrane and through contact between the opisthion and the posterior arch of the atlas. The paired alar ligaments, which run obliquely from the posterolateral surface of the odontoid to the medial occipital condyles, impart stability to lateral bending and rotation.³⁴ Studies have demonstrated that disruption of the tectorial membrane results in excessive flexion–extension and longitudinal displacement (> 1 cm) of the basion from the odontoid process. Compromise of the alar ligaments results in increased lateral bending and rotation. Frank occipitoaxial subluxation occurs when both the tectorial membrane and alar ligaments are disrupted.³⁹ In vivo clinical MR imaging data in children have demonstrated that involvement of the tectorial membrane is a critical threshold for instability in injuries involving the CVJ.⁴⁰ Larger paraspinous muscles have also been shown to contribute to the stability of the CVJ and are frequently involved in isolated or soft-tissue injuries.^{40,41}

The CVJ is the area of the pediatric spine that is most vulnerable to injury and potential instability. Injury to the O–C2 complex is the most common cervical spine injury in children less than 10 years of age.⁴² Several factors contribute to this susceptibility. First, articulations in the CVJ of a child are anatomically more predisposed to motion than those in adults. Second, as in the subaxial spine, the major stabilizing ligaments and paraspinous muscles are less developed and more elastic. Third, before approximately 8 years of age, the dentocentral synchondrosis between the odontoid process and the body of C2 is unfused. Generally, odontoid fractures in young children are actually epiphysiolysis of the growth plate at the dentocentral synchondrosis.⁴³ Congenital or chronic anomalies of the CVJ, such as os odontoideum and occipitalization of the atlas, can result in vulnerability to injury despite relatively minor trauma. The fulcrum of the cervical spine in infants and young children lies within the O–C2 complex as a consequence of the relatively large head size and short neck. Injuries to this region in children are mostly ligamentous or soft-tissue disruptions, rather than fractures, and are highly unstable.

60.3.3 Subaxial Spine

The stability of the subaxial spine is determined by (1) the ability of the vertebral bodies, facet joints, and intervertebral disks to withstand compressive forces and (2) the ability of spinal ligaments to withstand tensile forces.^{44,45} The pediatric subaxial spine is inherently more mobile than the adult spine, allowing considerably more movement at each vertebral segment in response to extrinsic forces. Several factors account for this hypermobility, including: (1) anterior wedging of the immature vertebral bodies, facilitating forward movement of adjacent motion segments^{14,25,26,46,47}; (2) shallow and more horizontally oriented facet joints, particularly in the upper cervical spine, requiring less force to elicit translation or flexion–extension^{14,25,26,46,47}; (3) absence of the unciniate process in children less than 10 years old, resulting in less restriction to lateral and rotational movements in the subaxial cervical spine⁴⁷; (4) more elastic spinal ligaments and joint capsules^{46,47}; (5) intervertebral disks that are more expansile in the longitudinal axis as a result of a higher water content^{48,49}; (6) epiphysiological growth zones at the vertebral end plates that split readily from the vertebral centrum under moderate shear forces⁵⁰; and (7) underdeveloped paraspinous muscles and a disproportionately large head that predispose to large degrees of motion in response to flexion–extension forces.

Within the subaxial spine, the upper cervical region is particularly hypermobile and is most susceptible to injury from flexion forces. The fulcrum for maximal flexion–extension in the subaxial cervical spine is at C2–3 in infants and young children and moves progressively caudal with increasing age until spinal maturity is reached.^{47,51,52} By 5 to 6 years of age, the fulcrum is at C3–4, whereas in adolescents and adults, it is located at C5–6. The elasticity of the interspinous ligaments in the developing spine is inversely proportional to age, accounting for the higher incidence of radiographic pseudosubluxation in the upper cervical spine of young children, most commonly at C2–3, but also seen at C3–4.^{53,54} Normal sagittal intervertebral translations of up to 4 mm can occur at C2–3 in children less than 12 years old. A 24% incidence of moderate to marked C2-on-C3 subluxation

has been demonstrated in children between 1 and 7 years old, whereas 46% of children less than 8 years old had 3 mm or more of anterior–posterior motion of C2 on C3 on flexion–extension studies.²⁵ Greater degrees of subluxation in the upper cervical spine should be considered unstable, and the normal upper limit of translation is 3 mm in the remaining subaxial spine. Children 12 years of age and older should not have physiologic motion greater than 3 mm.

60.4 Initial Evaluation and Treatment

Spinal column injury should be suspected in any child after trauma from an appropriate mechanism of injury (i.e., motor vehicle accident, fall, sporting accident) or with posttraumatic neurologic deficit. Initial management in the field and emergency department should always focus on maintenance of the airway, breathing, and circulation. The maintenance of adequate perfusion and blood oxygen levels immediately following trauma is of the utmost importance and may be more beneficial than any subsequent pharmacologic or surgical intervention.

During initial resuscitation efforts, appropriate immobilization of the patient's spine should be employed to prevent additional injury. In older children and adolescents, standard back board and cervical spine immobilization techniques can be used. In young children, however, the disproportionately large head may result in flexion of the cervical spine when the patient is immobilized in the supine position.⁵⁵ This should be avoided by bolstering the torso with padding or using a specialized board with a recess for the occiput. Use of a cervical collar is often problematic in infants; they are often best immobilized with the head and torso temporarily taped to the board. An underappreciated cause of avoidable distraction following immobilization is an inappropriately sized cervical collar. Log rolling should be used to move and position children with suspected spine injuries for diagnostic studies.

Several mechanisms of injury are significantly associated with spine injuries and should prompt complete screening radiographs. These include significant fall, pedestrian-versus-motor vehicle accident, abdominal lap seat belt injury, ejection from a motor vehicle, and suspected child abuse. Additionally, any child presenting with neck or axial back pain, neurologic deficit, or reduced mental status and an appropriate traumatic mechanism should be assumed to have a spinal column injury until it is proved otherwise. Several cutaneous findings that are associated with spinal column injuries include seat belt bruises of the abdomen and neck, subcutaneous emphysema, displacement of the spinous processes, and tire tracks across the back. Given the high incidence of both multiple contiguous and noncontiguous spinal column injuries in several series, the discovery of a spine injury at any level should trigger radiographic screening of the entire spinal column.^{3,10,11} Once a determination has been made that a spinal column injury is present, the same principles that apply to adult spine trauma are employed: (1) a determination of biomechanical instability, (2) closed or open reduction (and decompression) if necessary, and (3) appropriate spinal immobilization (external or internal).

60.5 Diagnostic Imaging

The combined use of common imaging modalities, including plain radiographs, targeted fine-cut CT, and MR imaging allows the clinician to identify both osseous and soft-tissue injuries and to make a determination regarding resulting instability. Of particular importance in the pediatric population is obtaining an accurate diagnosis while minimizing the exposure of the developing child to ionizing radiation. Ultimately, the treatment of pediatric spinal column trauma is based upon the neurologic status of the patient, diagnostic imaging results, and degree of maturation of the spinal column.

Plain radiographs are the mainstay of initial diagnostic imaging in any child with suspected spinal column trauma. Although specific guidelines exist for the radiographic assessment of adults with suspected spinal column trauma, there is still controversy regarding the appropriate indications for screening radiographs in children. Proposed pediatric protocols are usually aimed at ensuring that clinically significant injuries are not missed, while simultaneously limiting exposure to ionizing radiation. A prospective multicenter study by Viccellio et al in 2001 used the National Emergency X-Radiography Utilization Study (NEXUS) criteria to evaluate for cervical spine injury in children younger than 18 years.⁵⁶ The authors defined five high-risk criteria, including: (1) midline cervical tenderness, (2) evidence of intoxication, (3) altered level of alertness, (4) focal neurologic deficit, and (5) painful distracting injury. If any one of these criteria was met, the patient was considered high-risk; however, if none was met, they were low-risk. Of 3,065 children in the study, 603 (19.7%) were defined as low-risk, none of whom ultimately had a documented cervical spine injury. Conversely, there were 30 (0.98%) cervical injuries in the group of children considered to be high-risk. The results of this study clearly demonstrate that application of the NEXUS criteria to children reduces the need for screening cervical spine radiographs by almost 20% without resulting in any missed injuries.

The necessity and utility of open-mouth plain radiographs in pediatric trauma patients have been questioned.^{57,58} Current evidence suggests that the open-mouth odontoid view may not be routinely needed in children less than 5 to 9 years old.^{57,58} There is agreement that open-mouth views should be attempted in children 9 years of age and older. Conversely, dynamic imaging is of particular importance in the assessment of pediatric spinal column trauma. Ligamentous injury is more common than osseous injury in children and cannot be excluded based on the demonstration of normal bony anatomy on static radiographs; therefore, flexion–extension imaging should be obtained for responsive and cooperative patients during initial screening if spinal column trauma is suspected. In children unable to tolerate this, ligamentous injury may be assessed by using MR imaging with fat-suppressed sequences, or dynamic imaging may be attempted in a delayed fashion. Because the sensitivity of MR imaging to detect edema associated with ligamentous injury is reduced after 48 hours from spinal column trauma, the study should be obtained within this time interval in order to be diagnostic.⁵⁹ Ligamentous injury may also be assessed in a delayed fashion in unresponsive patients by using dynamic imaging under direct fluoroscopic guidance. In such patients, MR imaging should still be considered to rule out

an occult compressive lesion before dynamic imaging is obtained because the patient's neurologic examination cannot be followed reliably during flexion and extension.

MR imaging should be obtained in all children with a neurologic deficit and should also be considered before closed reduction and external immobilization or operative reduction and fixation to assess the degree of canal compromise. If the patient has previously implanted ferromagnetic instrumentation or intra- or paraspinal bullet fragments, CT myelography can be substituted for MR imaging to exclude compressive lesions.

CT should be used judiciously in the pediatric population in order to minimize exposure to ionizing radiation. It is not recommended as a means to clear the entire cervical spine, but its targeted use is helpful in evaluating osseous structures that are poorly visualized on plain radiographs. Many radiographic determinants of spinal column instability are difficult to assess accurately on plain radiographs, and in these cases further imaging with CT may be warranted. If an injury is suspected on plain radiographs, fine-cut CT should be obtained through the suspicious and adjacent levels to better define the anatomy, to survey for adjacent fractures, and to detect areas of incomplete ossification that may influence operative management.

60.5.1 Radiographic Determinants of Craniovertebral Junction Instability

Plain radiographs provide the most practical method of determining instability at the CVJ. Several radiographic criteria have been developed based on distances between osseous structures as seen on X-ray imaging (► Fig. 60.1). When visualization of these structures is poor, accurate assessment of CVJ instability may require CT of the O–C2 complex. It is important to note that extrinsic forces, such as positioning and immobilization, in highly unstable CVJ injuries may influence the anatomical relationships of the bony elements following injury. In children, these forces tend to be flexion due to the large head size in relation to the torso and distraction from a cervical collar. Additionally, plain film measurements have traditionally exhibited variation in response to differing magnification from discrepancies in film-to-target distances. The Powers ratio, Lee X line, and C1–2:C2–3 ratio were originally designed as dimensionless measurements to address this issue. However, with the widespread use of digital radiographic collection and processing systems, this problem has been mitigated. When instability of the O–C2 complex is suspected, it is imperative to use the following criteria in combination to attain a complete and thorough assessment. Only one positive finding should be considered necessary and sufficient for a diagnosis of CVJ instability.

Occipital Condyle–C1 Joint Interval

The O–C1 joint interval (CCI) is the distance between the occipital condyle and the superior facet of C1 (► Fig. 60.1a). Based on plain films, Kaufman et al found that this interval in children should not exceed 5 mm between any opposing points of the joint articulation on lateral or anteroposterior views.⁶⁰ Interpretation of the CCI on X-ray is nearly impossible, however,

because of superimposition of the mastoids and the imperfect overlap of the two O–C1 joints.

This difficulty is overcome with thin-cut CT. Using this modality, Pang et al established 4 mm as the upper limit of normal for the CCI in children.^{61,62} In a series of 89 normal children, the mean combined CCI for all 178 joints was 1.28 ± 0.26 mm, with no single CCI larger than 1.95 mm.^{61,62} Sagittal–coronal variation of the CCI is approximately 12%, and left–right variation is less than 3%. No individual measurement in any projection exceeded 2.5 mm. By using 4 mm as the upper limit of normal for the CCI, Pang et al subsequently demonstrated that at least one and usually both O–C1 joints were separated in all children with proven atlanto-occipital dislocation (AOD) regardless of Traynelis classification.⁶³ These children often had horizontal displacement or fractures of the O–C1 joint in addition to longitudinal separation. Coronal reconstruction through the occipital condyles demonstrates the true extent of AOD, with asymmetry suggesting a rotary component to the displacement. The CCI is the only measurement that directly measures the O–C1 articulation and is considered by most authors to be the single most reliable diagnostic criterion for O–C1 instability.

Dens-Basion Distance

The dens–basion (DB) distance of Wholey et al is the oldest criterion for determining O–C1 instability and is the distance between the tip of the odontoid process and the basion in the sagittal plane (► Fig. 60.1b).⁶⁴ The upper limit of the DB distance is 5 mm in adults and between 10 and 12.5 mm in children.⁶⁵ The marked difference in the DB distance with age is attributable to the incomplete ossification of the apical dens in children.⁶⁴ Recent data exclusively from children indicate that the normal value is less than 12.5 mm; in 11 children with proven AOD, all DB distances were greater than 14 mm.⁶⁵ One significant problem with the DB distance that has historically limited its utility is that its measurement on plain X-ray is influenced by the film-to-target distance. Additionally, variable ossification of the apex of the odontoid process between 2 and 12 years of age makes application of the DB distance potentially problematic in children. Finally, the DB distance varies with flexion, extension, and the application of axial traction in normal subjects. Nevertheless, a DB distance of more than 14 mm in a child should be considered diagnostic of O–C1 instability.

Basion–Axial Interval

First reported by Harris et al in 1994 to describe the translational relationship between the occiput and C2 in AOD, the basion–axial interval (BAI) is the distance between the basion and a line extending rostrally from the dorsal cortex of the odontoid process (the posterior axial line) (► Fig. 60.1c).⁶⁶ In adults, the BAI normally extends from 12 mm anterior to 4 mm posterior to the posterior axial line (+12 mm to –4 mm) and does not change with flexion or extension. In children, the BAI is usually less than 12 mm anterior to the posterior axial line, but the basion does not extend posterior to the posterior axial line as it does in adults.⁶⁶ The BAI exceeds +12 mm in Traynelis type I (anterior) AOD, whereas it is less than –4 mm in Traynelis type



Fig. 60.1 Radiographic determinants of craniocervical junction instability. (a) Occipital condyle–C1 (O–C1) joint interval (CCI). The mean CCI is determined by measuring and averaging the distance across the joint space at four equidistant points (white arrowheads) along the occipital condyle and C1 superior articulating facet. The CCI is considered by most authors to be the single most reliable criterion of O–C1 instability, and a value ≥ 4 mm is considered abnormal.^{61,62} (b) Dens–basion distance. Measured from the dens (D) to the basion (B), distances of 5 and 12.5 mm are the upper limits of normal in adults and children, respectively.⁶⁴ A value > 14 mm in children is diagnostic for O–C1 instability.⁶⁵ (c) Basion–axial interval (BAI). This is the distance between a vertical line drawn through the basion and the posterior axial line (PAL; white arrowheads); it is usually $< + 12$ mm (anterior to the PAL) in normal children.⁶⁶ (d) Powers ratio. The ratio is determined by dividing the distance between the basion (B) and the midpoint of the posterior arch of C1 (C) by the distance between the opisthion (O) and the midpoint of the anterior arch of C1 (A).⁶⁸ Normal values typically are 0.77 ± 0.09 , with a value > 1 indicative of anterior atlanto-occipital dislocation (AOD).^{29,69} (continued)

III (posterior) AOD.⁶³ Used in conjunction with the DB distance, the BAI is more accurate in adults than either the Powers ratio or the Lee X line.⁶⁷ In young children, however, the posterior cortical margin of the odontoid process is anteriorly sloped, artificially moving the reference point for the BAI forward. As a result, the BAI may underestimate the degree of anterior occipital translation in AOD.

Powers Ratio

The distance from the basion to the posterior arch of the atlas (BC) divided by the distance from the opisthion to the anterior arch of the atlas (OA) is the Powers ratio (► Fig. 60.1d).⁶⁸ In the normal population, the ratio is 0.77 ± 0.09 , with all ratios over 1 being abnormal and indicative of anterior (type I) AOD.^{29,69}

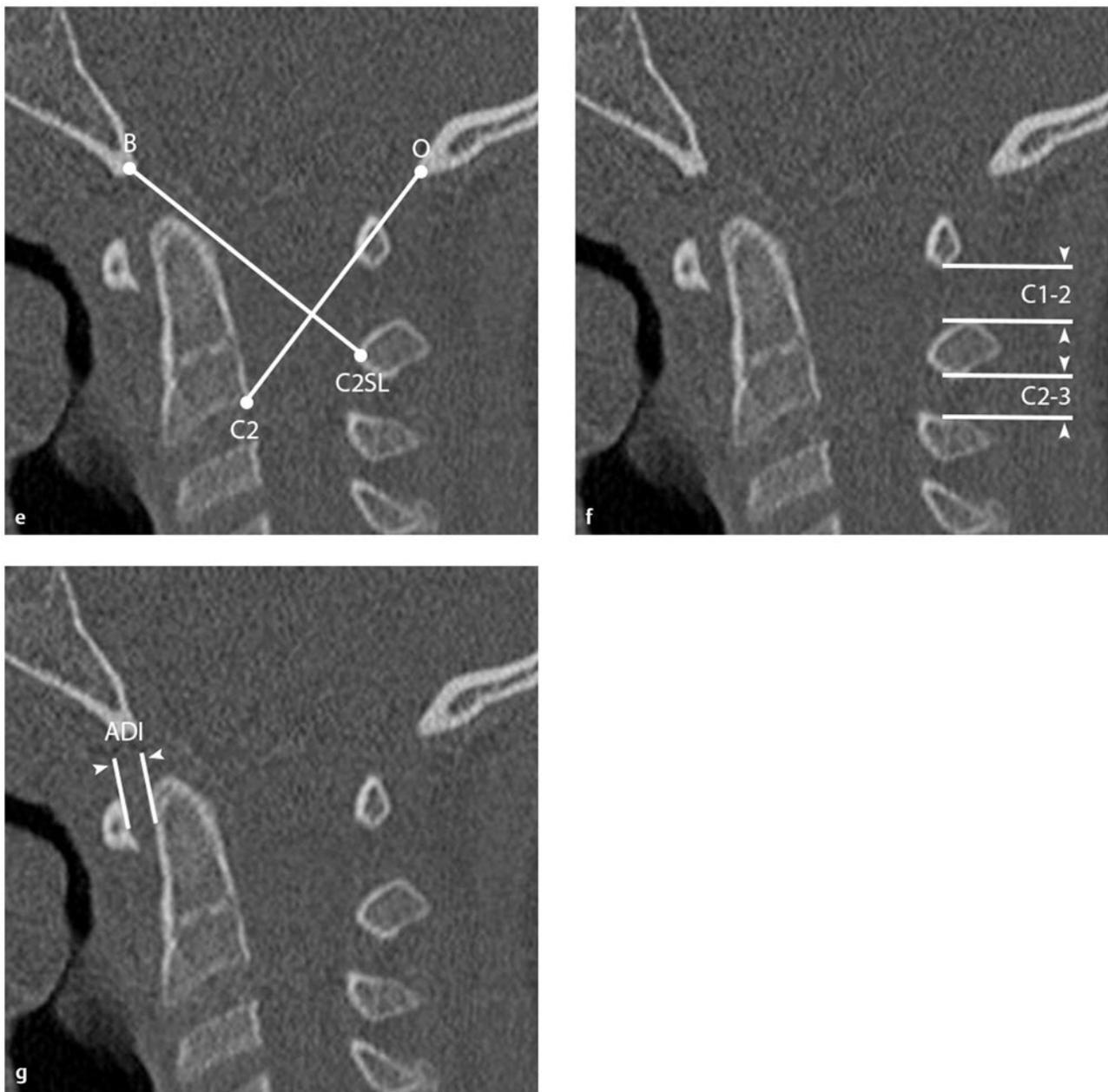


Fig. 60.1 (continued) (e) Lee X line. Lines from the basion (B) to the midpoint of the C2 spinolaminar line (C2SL) and from the opisthion (O) to the posteroinferior body of C2 are drawn.⁷⁰ The first line should tangentially intersect the posterosuperior dens, and the second should intersect the highest point on the C1 spinolaminar line. At least one intersection should be present; if neither is present, AOD should be suspected. This is of limited utility in children because it requires a fully formed odontoid process to be accurate. (f) Atlantodental interval (ADI). The distance between the anterior arch of C1 and the ventral surface of the dens (white arrowheads) should be < 3 mm in adults and 5 mm in children older than 8 years.^{28,54,71,72} Values greater than these suggest transverse ligament compromise. (g) C1-2:C2-3 ratio. This is obtained by dividing the shortest distance between the posterior arch of C1 and the spinous process of C2 by the shortest distance between the spinous processes of C2 and C3 (white arrowheads).⁴⁰ Damage to the tectorial membrane may result in ratios > 2.5.

In anterior AOD, the ratio is increased because BC widens while OA shortens. Two major disadvantages of the Powers ratio are a failure of the measurement to properly diagnose posterior and longitudinal (types II and III) AOD and the fact that in children up to 70% of lateral cervical spine films may not reveal the exact position of the opisthion.⁶⁹ The use of sagittal CT reconstructions to properly localize the opisthion may be necessary.

Finally, anomalies of the posterior arch of C1 and the foramen magnum can make the Powers ratio invalid.

Lee X Line

Proposed by Lee et al in 1987, the X line does not require calculation.⁷⁰ On a lateral cervical radiograph or sagittal CT, two

lines are drawn: one from the basion (B) to the midpoint of the C2 spinolaminar line (C2SL) and a second from the postero-inferior body of C2 to the opisthion (O) (► Fig. 60.1e). The result is an X in which the basion-to-C2SL line should tangentially intersect the posterosuperior dens and the C2-to-opisthion line should tangentially intersect the highest point on the C1 spinolaminar line. At least one intersection should be present; if both lines fail to intersect, then AOD should be suspected. The Lee X line is of limited utility in children, however, as its validity depends on atlantoaxial integrity and a fully developed odontoid process.

C1–2:C2–3 Interspinous Ratio

The C1–2:C2–3 interspinous ratio of Sun et al is determined by dividing the shortest distance between the lower cortex of the posterior C1 ring and the upper cortex of the C2 spinous process by the corresponding shortest distance between the spinous processes of C2 and C3 (► Fig. 60.1f).⁴⁰ This ratio was developed because instability of the CVJ may manifest as separation of C1–2 as well as O–C2. The proposed mechanism whereby AOD results in an abnormal C1–2:C2–3 ratio is that a loose O–C1 articulation allows forward and downward pressure of the occipital condyle on the anterior rim of the superior facet of C1, resulting in separation of the posterior arch of C1 away from C2.⁴⁰ Ratios greater than 2.5 suggest damage to the tectorial membrane.⁴⁰ The C1–2:C2–3 ratio has several limitations. First, the relationship between the occipital condyles and the anterior rim of C1, and therefore the C1–2 interspinous distance, can be altered to an unpredictable degree by the mode of temporary immobilization used following injury. Second, concomitant rupture of the transverse ligament causes C1–2 subluxation, altering and invalidating the ratio, as will congenital anomalies of the posterior arches of the upper cervical vertebrae. Third, the ratio may be artificially enlarged by the use of muscle relaxants.

Atlantodental Interval

The most commonly used radiographic criteria to assess instability at C1–2 is the distance between the dorsal cortex of the anterior arch of C1 and the ventral aspect of the odontoid process, the atlantodental interval (ADI) (► Fig. 60.1g). Widening of the ADI results from failure of the transverse ligament. The normal upper limit of the ADI is 3 mm in adults and 5 mm in children less than 8 years old.^{71,72} In the setting of a C1 fracture (Jefferson fracture), rupture of the transverse ligament should also be suspected if the bilateral overhangs of the C1 lateral masses on an anteroposterior view total 7 mm or more.⁷³

60.5.2 Radiographic Determinants of Subaxial Spine Instability

The guidelines for determining overt instability in the pediatric subaxial spine are not well defined. Stability can be predicted radiographically in two main ways: (1) by using a simplified biomechanical model as either a two- or three-column structure or (2) based on the degree of segmental angulation or horizontal displacement at the suspected injury levels. Both the two- and three-column models, however, are biomechanical

simplifications developed from studies of the mature adult spine. The developing pediatric spine, with its unique anatomy and biomechanics, is not ideally represented by either of these models.

Radiographic assessment of the amount of horizontal displacement and degree of segmental angulation at the levels of suspected injury can provide additional information. Although the criteria are still poorly defined, more horizontal displacement, but less angulation, is typically allowed in a normal, stable pediatric spine because of its inherently greater ligamentous laxity and elastic recoil compared with an adult spine. In children younger than 8 years, horizontal displacement of up to 4.5 mm should be considered normal.²⁹ In children older than 8 years, horizontal displacement of more than 3.5 mm is generally considered unstable. On radiographic imaging of the subaxial spine, the upper limit of angulation between adjacent vertebrae that suggests ligamentous injury in children is commonly reported as 7 degrees. If a child has angulation that is less than 7 degrees with severe pain and muscle spasm, external immobilization (i.e., a hard cervical collar) should be considered until satisfactory dynamic studies can be obtained to rule out instability. For children with angulation between 7 and 11 degrees and without a neurologic deficit, flexion–extension studies should be obtained to assess stability. If the degree of angulation is unchanged on dynamic imaging, the study should be repeated in several days to eliminate confounding from muscle spasm. If repeated imaging demonstrates less than 11 degrees of angulation and the study is satisfactory (i.e., the child is without muscle spasm and is able to obtain at least 30 degrees of flexion–extension), external immobilization should be pursued until dynamic radiographs are obtained to confirm healing of ligamentous structures. If ligamentous injury is chronic or will not heal with immobilization, surgical stabilization may be necessary.

Cervical Spine Clearance

Currently, no national guidelines exist for clearance of the cervical spine in children after trauma. The most recent American Association of Neurological Surgeons and Congress of Neurological Surgeons joint guidelines for the management of pediatric cervical spine and spinal cord injury stated that there was insufficient evidence to establish standards of care for the diagnosis of cervical spine injuries in children.⁵⁹ Despite this, several protocols have been published to assist in clearance of the cervical spine in children.^{74–76} The use of defined protocols decreases the time needed to clear the cervical spine in children,⁷⁷ reduces the number of missed injuries,⁵⁶ and facilitates clearance by non-neurosurgical medical staff.^{74,76} Obtaining a consensus for a universal protocol is challenging, however, given the involvement of numerous different health care providers (neurosurgeons, trauma surgeons, orthopedic surgeons, emergency department physicians, and others) who have differing training and experience.

Brockmeyer et al recently published the results of a pilot study examining the prognostic value of plain radiographs, flexion–extension radiographs under fluoroscopy, CT, and MR imaging in clearing the pediatric cervical spine after severe trauma.⁷⁵ The authors determined that within this high-risk population there is an overall low prevalence (4%) of instability. Plain radiographs, flexion–extension radiographs, and CT all

had very high rates of sensitivity and specificity in screening for unstable cervical injuries. MR imaging also demonstrated a high sensitivity but had a more significant false-positive rate.

We previously published a protocol for cervical spine clearance in communicative children between 3 and 18 years old to facilitate clearance by non-neurosurgical personnel.^{74,78} The protocol is based on the NEXUS data demonstrating that approximately 20% of children fall into a low-risk category for cervical injury after trauma.⁵⁶ If initial screening radiographs are abnormal, a neurosurgical consult is obtained. If imaging is normal, the NEXUS criteria are then applied to facilitate clearance of the cervical spine. Communicative children with normal radiographs and meeting the low-risk NEXUS criteria are cleared. Failure to meet all five of the low-risk criteria in a child with a normal neurologic examination prompts additional investigation with dynamic imaging. The cervical spine is cleared if the results are normal. If abnormal, the patient is referred to neurosurgery for assistance with clearance. Our protocol simplifies the method used for pediatric cervical spine clearance, allowing clearance in approximately 60% of cases to be performed by non-neurosurgical personnel without any missed injuries. Abnormal plain or dynamic radiographs, or an abnormal neurologic examination, should prompt immediate neurosurgical referral and further imaging with CT and MR imaging, as appropriate.

Clearance of the cervical spine in noncommunicative children, including those between 0 and 3 years of age, is particularly difficult because it is usually not possible to apply the NEXUS criteria in these patients. In particular, the incidence of ligamentous injury is higher in younger, noncommunicative children than in older, communicative children.^{12,74,79,80} To address this issue, we subsequently developed a protocol for cervical spine clearance in this population.⁷⁶ The overwhelming majority of noncommunicative children can be cleared without the need for either CT or MR imaging, and flexion–extension radiographs are only rarely needed. In more than 80% of cases, the cervical spine is able to be cleared based on a combination of normal plain radiographs and a benign clinical examination. In more than 500 evaluations, the protocol resulted in no missed injuries.

60.6 External Immobilization

The vast majority of children with spinal column trauma do not require surgical intervention and can be effectively managed with external immobilization. Examples of injuries that are often amenable to initial treatment with external immobilization include the following: C1 (Jefferson) fractures in which there is minimal ligamentous disruption and the transverse ligament remains intact (per the “rule of Spence”⁷³ with a C1 lateral overhang of 7 mm or less on odontoid view radiographs or coronal CT); atlantoaxial rotatory subluxation/atlantoaxial rotatory fixation (AARS/AARF); acute odontoid fractures with minimal displacement or angulation; C2 pedicle (hangman) fractures; purely ligamentous injuries of the subaxial cervical spine without gross instability; osseous anterior and posterior column injuries of the subaxial spine without gross instability or kyphotic deformity; thoracolumbar compression fractures; thoracolumbar burst fractures without neurologic deficit or

instability; flexion–distraction injuries without neurologic deficit or significant ligamentous injury (kyphosis < 20 degrees); low-grade spondylolysis/spondylolisthesis; and SCIWORA. The presence of a progressive neurologic deficit from a compressive lesion and evidence of gross instability are contraindications to primary management with external immobilization alone and are indications for surgical intervention. Early mobilization of a child after placement in an external immobilization device is important. The intensity and duration of external immobilization must be customized to each child. These depend upon the injury type, degree of reduction required, patient compliance, activity level, and evidence of radiographic fusion.

60.6.1 Craniocervical and Cervical Immobilization

Halo Ring and Vest

A properly fitted halo ring with pins and vest provides the most rigid external immobilization of the cervical spine and is the gold standard orthosis in children with an unstable cervical injury.^{81,82} Newer halo orthoses without pins are also available. A halo is particularly suited for immobilization of the CVJ and upper cervical spine. An advantage of the halo system is that it causes the least interference with mandibular motion and eating; it is the only external cervical orthosis that does not require chin support.⁸³ Additionally, the halo ring provides a means to apply traction in order to obtain either closed or open reduction. Disadvantages include complications such as pin loosening or infection, the potential for injury (i.e., skull fracture) in children prone to detrimental behavior (frequent falls or altercations during which the halo may be used by another as a handle or by the wearer as “attack antlers”), and the morbidity associated with placement and a prolonged duration of use (i.e., difficulties with hygiene).

A halo ring is best applied in young children under general anesthesia or conscious sedation with cardiopulmonary monitoring. In compliant adolescents, it may be applied with only local anesthesia if necessary. Halo immobilization can be achieved even in very young children who are at least 1 year old. The forces used must be reduced and dissipated through more contact points when a halo ring is applied in a child less than 6 years old. In infants younger than 2 years, 10 pins (as opposed to 4 pins in older children and adults) should be used and finger-tightened only. From ages 2 to 6, the number of pins can be reduced to 8, starting with 2 inch-pounds of torque for a 2-year-old with an increase of 1 inch-pound per year up to age 6. Past this age, 4 pins may be used and should be tightened to 8 inch-pounds of torque, as in adult patients. Although they are necessary to prevent iatrogenic skull fracture, a disadvantage of using more pins in younger children is that there are fewer unused holes on the ring to allow pin changes in cases of infection or loosening at the pin site. Pins may loosen by up to 4 inch-pounds of torque within the first day after insertion or after halo vest uprights are attached. Pins should therefore be tightened 24 hours after insertion and again after attachment of a halo vest and uprights if this is not done at the same time as ring placement (such as when halo traction is attempted). Because most cervical injuries are unstable in flexion, it is often preferable to immobilize the spine in mild extension; however,

some children may be displeased with this positioning. In these cases, a “military” posture, in which posterior translation is substituted for extension, may be better tolerated. In the rare cases of very young children who are too small for a vest, a halo ring attached to rods incorporated into a thoracic cast may be required.

The incidence of complications associated with halo immobilization is higher in children than in adults; however, the majority of these are pin loosening and pin site infections.^{84,85} The higher rate of pin loosening in children is likely related to the thin calvaria. Skull fractures can be avoided by using more pins for placement, as described above, and by placing anterior pins in the superolateral orbital buttress above the eyebrows.⁸⁴ The calvaria is thicker in this location, and such placement also avoids inadvertent injury to the supraorbital and supratrochlear nerves. The incidence of pin loosening and infection correlates with the duration of halo fixation. One study reported an overall complication rate of 68% in children undergoing halo immobilization.⁸⁶ The anterior pins were responsible for the majority of pin site complications, with younger children more likely to experience pin loosening and older children more likely to experience pin site infections.⁸⁶ Alignment slippage also affects children with halos more than adults. This may be due to undiagnosed pin loosening or the fact that children are less likely than adults to appropriately protect their halos.²⁹

The age of the patient largely determines the appropriate management of loose halo ring pins. Retightening of loose pins should be avoided in young children because they typically have thin calvaria with soft bone surrounding the pin site as a result of accelerated osteoclasts. Pin retightening may result in full-thickness penetration of the skull and intracranial abscess formation.⁸⁷ In these children, loose pins should be removed and replaced with a pin at a new site. In contrast, pin retightening is generally safe in older children as long as resistance can be felt during tightening.

Pin site infections are more common in children than in adults, with a reported incidence in one series of 31% versus 6%, respectively.⁸⁴ Infected pin sites should be managed by removing all scabs to allow drainage and by cleaning thoroughly with 10% hydrogen peroxide solution four times daily. Oral antibiotics are appropriate treatment for mild superficial infections if the pin site is still tight. If pin loosening is noted, or if the infection is more severe and associated with erythema, swelling, purulent drainage, pain, or headaches, the pin should be removed and replaced at a new site and intravenous antibiotics considered to prevent osteomyelitis of the skull. Screening CT should be considered to assess for intracranial abscess.^{87–89}

Minerva Brace

The Minerva brace does not use cranial pin fixation and is a useful method of cervical immobilization in children who cannot tolerate halo placement.⁹⁰ The mandibular strap allows movement to facilitate eating; therefore, the rigidity of fixation is inferior to that of a halo. To address this, a hybrid of the halo and Minerva brace has been developed that incorporates a molded cranial ring as opposed to pins and attaches to a molded vest with malleable rods.⁹¹ Other disadvantages of the Minerva brace include a large surface area in contact with the molded brace that can result in skin irritation and breakdown,

and the ease with which children may escape from the brace compared with a halo. Additionally, a Minerva brace is not suitable for the application of traction to the cervical spine.

Rigid Cervical Collar

The rigid cervical collar is the most common and practical of cervical orthoses. Compared with a halo or Minerva brace, it provides less stability in the upper cervical levels but similar stability in the lower cervical spine. It is the orthosis of choice for the immediate cervical immobilization of anyone but infants or very young children in the acute trauma setting. A rigid cervical collar may also be used in children with cervical fractures, particularly of the subaxial cervical spine, that do not require surgery or the degree of rigidity afforded by a halo or Minerva brace. A hard collar provides adequate immobilization in compliant older children and adolescents following craniocervical or cervical internal stabilization and fusion. The main disadvantage of this type of orthosis is that it can be easily removed. Removal by younger children may be prevented by the use of duct tape.

Posted Cervical Orthoses

There are many additional types of cervical orthoses that attach to the thorax via buckles and straps and provide immobilization through the use of posts or cups that are secured to the occiput and mandible. The main benefits of these orthoses are that they provide a greater degree of fixation than a rigid cervical hard collar and are more difficult for children to remove. A prime example is the Guilford brace, which is advocated by Pang and colleagues for external immobilization in children with cervical SCIWORA.^{9,29,92} The limitation of middle and lower cervical spine flexion, extension, and rotation provided by the Guilford brace is similar to that of other cervicothoracic orthoses, as is its relative ineffectiveness at inhibiting lateral bending.⁸¹ The main advantage of the Guilford brace is that it can be customized within 24 hours to fit any child down to 1 year of age. The Guilford brace is also suitable for external immobilization following reduction of AARF.

Molded Shells

Shells made of molded thermoplastic materials are useful for neonates and infants who require external immobilization of the cervical or upper thoracic spine. These types of orthoses are designed to conform to the back of the torso and head and are secured to the patient with self-adhesive straps across the torso and forehead.²⁹ The open design allows nursing, changing, and placement in a car seat.

60.6.2 Thoracolumbar Immobilization

The two main types of orthoses used for external immobilization of the thoracolumbar spine are the Jewett brace and the molded thoracolumbosacral orthosis (TLSO). The Jewett brace is used to provide hyperextension in the treatment of traumatic kyphotic deformity. A TLSO is appropriate for external immobilization of the thoracolumbar spine when hyperextension is not required. A last resort for external immobilization in very young children who are not compliant with a TLSO is casting of the torso and legs.

60.7 Internal Stabilization and Fusion

60.7.1 General Principles

Children with traumatic spinal column injuries who present with progressive neurologic deficits or evidence of gross instability should undergo prompt surgical intervention. In some cases, such as a traumatic herniated disk or apophyseal avulsion fracture in which there is localized neural element compression without significant trauma to the rest of the spinal column, simple decompression may be all that is required. In many instances, however, surgical intervention will necessitate the incorporation of internal stabilization and fusion procedures to provide immediate immobilization of unstable spinal column segments. Examples of traumatic spinal column injuries in which internal stabilization and fusion should be considered include the following: AOD; C1 (Jefferson) fractures in which there is compromise of the transverse ligament (C1 lateral overhang of >7 mm on odontoid view radiographs or coronal CT); C1–2 (atlantoaxial) subluxation; AARS/AARF that involves anterior translation of the atlas (Field-Hawkins types II and III), is chronic, or is recurrent; odontoid fractures that cause spinal cord compression or that fail to fuse after external immobilization; hangman (C2 pars) fractures that cause significant ligamentous injury or that fail to heal after external immobilization; multiple thoracolumbar compression fractures with progressive kyphosis; thoracolumbar burst fractures with instability or neurologic deficit; flexion–distraction injuries with neurologic deficit or significant ligamentous injury (more than 20 degrees of kyphosis); fracture–dislocation injuries; and refractory, progressive, or high-grade spondylolysis/spondylolisthesis.

The primary benefit of internal instrumented fusion is immediate immobilization of the unstable segments of the spinal column. This reduces the risk for subsequent deformity, pain, and injury to the underlying spinal cord or nerve roots from progressive instability. Additionally, for those patients with injuries for which initial treatment with an external orthosis may be considered, internal stabilization and fusion often allow the elimination of, or a reduction in, the duration or degree of intensity of external immobilization. The primary disadvantages of instrumented fusion in children include the risks inherent to general anesthesia and the procedure itself, and poorly understood alterations of spinal growth in young children.

Operative intervention in children with a progressive neurologic deficit should be performed expeditiously to decompress the spinal cord or nerve roots and to maximize potential neurologic recovery. In children with no evidence of neural compression but with gross instability or malalignment, definitive surgical intervention is generally not as urgent as long as adequate immediate stabilization has been achieved. Any attempts at closed reduction should be performed manually in the operating room with the use of general anesthesia, fluoroscopy, and spinal cord monitoring (if available). In the setting of cervical cord compression or an unstable cervical spine injury, awake fiber-optic intubation is preferred, although vigorous resistance by a child may increase the risk for injury to the cervical cord. In these cases, fiber-optic nasotracheal intubation following the induction of general

anesthesia is a viable alternative. Prepositioning somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) should be obtained following intubation when there is significant instability or spinal cord compression. SSEP and MEP monitoring should be continued after positioning and throughout the duration of the surgery, if possible.

In young children who still have a significant amount of spinal growth remaining, it is particularly important to limit the number of instrumented spinal segments. This should be balanced against the desire to select a fusion construct that will achieve the greatest immediate internal stability. In children, a greater burden is often placed upon the immediate strength of the instrumented fusion construct, particularly in those with upper cervical spine injuries. This is because non-halo orthoses are more frequently used postoperatively in this population given the higher complication rates seen with halo immobilization. Another issue of particular importance in pediatric patients undergoing internal stabilization and fusion is the inadvertent inclusion of normal adjacent segments into the fusion mass. Callus formation and subsequent fusion following violation of the periosteum and immobilization of the spine are more exuberant in children than in adults, particularly in the relatively immobile thoracic spine. The subperiosteal dissection of adjacent segment laminae and spinous processes and migration of fusion material into these sites are a likely cause of such “fusion creep.” This results in an unnecessary loss of mobility and a theoretically increased risk for adjacent segment degeneration resulting from a greater lever arm and increased stress at the ends of the fusion mass. Inadvertent incorporation of the occiput into an atlantoaxial fusion results in loss of up to 13 degrees of flexion–extension at the O–C1 joint, and inadvertent fusion of a cervical level below C2 results in loss of 8 to 17 degrees of flexion–extension and 8 to 12 degrees of rotation, depending on the level and the age of the patient.⁹³ Meticulous subperiosteal dissection limited as much as possible to the levels to be fused is the most efficient method to prevent inadvertent extension of the fusion mass.

Care must also be taken during dissection of the pediatric spine to avoid inadvertent entry into the spinal canal through the midline cartilaginous tissue between nonfused laminae, which is easily disrupted by monopolar electrocautery. The surgeon must be aware that the possibility of nonfused laminae exists despite maximal spinal column maturation and should not assume complete ossification at a given level despite complete ossification at other levels. Fusion of the laminae occurs postnatally; it begins in the lumbar spine, proceeds cranially, and is usually complete by 3 years of age. Nonfused laminae are most prevalent at the rostral and caudal ends of the spinal column, occurring at S1, L5, C1, C7, and T1, in order of decreasing frequency. In addition to careful dissection, a discerning review of the preoperative imaging may help prevent inadvertent entry into the spinal canal through a midline defect of the posterior elements. In addition to nonfused laminae, the spinous processes are often poorly formed before fusion of their secondary ossification centers, precluding the successful use of interspinous wiring techniques. Also, transverse process hooks are usually not a viable option in children because of incomplete ossification.

The use of autologous bone grafts in children undergoing internal stabilization results in increased fusion rates compared with the use of allograft only. When possible, the use of autograft should be considered, particularly when large structural bone grafts are required, such as for occipitocervical or atlantoaxial fusion constructs. Iliac crest remains the gold standard for autograft, although other autologous sources include the ribs, fibulae, and split-thickness occipital bone.²⁹

60.7.2 Craniovertebral Junction Instrumentation

Given the unique anatomy of the O–C2 complex, different techniques are required for internal stabilization and fusion of this region compared with the subaxial spine, including wire-graft techniques, C1–2 transarticular screws, Goel-Harms constructs, and odontoid screws. Given the high degree of flexion–extension at O–C1 and rotation and translation at C1–2, any fusion technique used at the CVJ must be able to adequately withstand forces directed in all four of these planes of motion.²⁹

Wire–Graft Techniques

Several techniques have been developed for C1–2 wiring given that the atlas lacks a spinous process for interspinous wiring and there is usually a large gap between the posterior arches of C1 and C2, so that the use of a structural bone graft is required to impart the necessary stability in extension unless the posterior arches can be firmly approximated. Additionally, the atlantoaxial joint subserves a high degree of rotation and translation; therefore, any C1–2 fusion construct must be able to withstand these forces as well.

Introduced in 1939, the Gallie fusion is the oldest published method for obtaining a C1–2 fusion construct through sublaminar wiring.⁹⁴ A single midline sublaminar wire is looped around the arch of C1 and the spinous process of C2, securing a structural bone graft positioned on the spinous process of C2 and against the dorsal aspect of the posterior arch of C1. The main disadvantage of this construct is that it lacks stability in both extension and rotation. Additionally, in children less than 12 years old, there is the potential for the midline wire to cut through the posterior arch of C1 at the midline synchondrosis.

The Brooks fusion, with modifications by Griswold et al in 1978, offers a greater biomechanical advantage than the Gallie fusion, obtaining stability in both flexion and extension and increased resistance to rotation and translation.⁹⁵ This construct is formed by passing bilateral sublaminar wires around the posterior arch of C1 and the laminae of C2. The wires are tightened over a corticocancellous bone graft that is “T-shaped” to prevent displacement into the spinal canal and wedged between the posterior arches of C1 and C2.⁹⁶ Stability in flexion is provided by the sublaminar wires, and in extension by the wedged bone graft.⁹³ Friction from the bone graft helps prevent rotation and translation at the atlantoaxial joint. In a more recent modification of the Brooks fusion, two separate bone grafts are placed between the posterior arches of C1 and C2 on either side of midline,⁹⁷ so that this fusion method can be used when the middle one-third of the posterior arch of C1 has been removed for decompression of the spinal cord. A disadvantage of this modification,

however, is that it requires the passage of two sublaminar wires (instead of one) around C1 and C2 on either side, potentially increasing the risk for cord injury during surgery.

The Dickman-Sonntag fusion is a combination of the Gallie fusion and the original Brooks fusion.⁹⁸ A single midline loop of wire is passed around the posterior arch of C1 and tightened around the spinous process of C2. This secures in place a structural bone graft that has been sized to fit snugly between the arches of C1 and C2, resting on the spinous process of C2. Advantages over the Gallie fusion are that in addition to stability in flexion from wiring, the Dickman-Sonntag fusion provides stability in extension from wedging of the graft between the posterior arches. Like the Brooks fusion, the Dickman-Sonntag construct prevents rotation and translation. An advantage of this technique over the Brooks fusion is that only a single loop of wire needs to be passed around the posterior arch of C1, where there is typically ample space. Therefore, it reduces the total number of sublaminar wires needed and completely avoids sublaminar passage at C2.

Instrumented Fusion

Instrumentation at the CVJ provides superior immediate stability compared with wiring techniques alone, allowing a reduction in the duration and intensity of postoperative immobilization. These techniques have been typically employed in older children who have a sufficiently developed anatomy to accommodate instrumentation; however, advances in instrumentation and techniques continue to allow hardware to be placed in progressively younger patients. Novel flow diagrams may assist with the selection of rigid internal fixation constructs in pediatric patients requiring occipitocervical or atlantoaxial stabilization.⁹⁹ Relatively long-term data suggest that there is no increased risk for cervical spinal deformity, subaxial instability, or significant growth inhibition in younger, compared with older, children following O–C2 or C1–2 fusion incorporating transarticular screw fixation.¹⁰⁰

Occipitocervical Fixation

Occipitocervical fixation is indicated in children with atlanto-occipital instability and generally consists of an occiput-to-C2 fusion. The main concern with fusion to the occiput in children is the relatively thin calvaria in comparison with that of adults. The occipital bone in young pediatric patients may be thick enough to enable sufficient screw purchase only in the midline keel or laterally near the mastoid processes. Plating systems that use screws with larger head diameters are useful to dissipate forces on the thin occipital bone. Additionally, an “inside-out” occipital screw technique has been developed that can be used in children to minimize the risk for intracranial injury from occipital screw placement.¹⁰¹ Postoperative immobilization with a rigid cervical collar is generally sufficient following occipitocervical fusion with rigid instrumentation.

C1–2 Transarticular Screws

Pioneered by Magerl in 1979, transarticular screws provide excellent stability in both rotation and translation across the C1–2 joint.¹⁰² The use of transarticular screws obviates the need for

postoperative halo immobilization in most cases, which is of obvious benefit in young children. Fusion rates are superior to those of wire-graft techniques with postoperative halo immobilization (95 to 98% vs. 80 to 86%, respectively).^{97,103,104} Wang et al reported a 100% fusion rate with no need for postoperative halo and no complications, compared with an 84% fusion rate reported by Lowry et al when fixation was obtained via wire-graft techniques and halo immobilization.^{105,106} Another advantage of transarticular screws is that they can be used for atlantoaxial fixation even in cases in which the posterior arches of C1 and C2 have been removed for decompression. If the arches of C1 and C2 remain intact, transarticular fixation can be supplemented with wire-graft techniques to afford even greater stability in flexion-extension.¹⁰⁷ Additionally, if subaxial spine fixation is needed, the construct can be easily extended to include lateral mass screws.

The main disadvantages of C1–2 transarticular screw fixation are that it is technically demanding and that the anatomy in young children may preclude safe screw placement. Preoperative planning of the screw trajectory is required, and intraoperative guidance with fluoroscopy or frameless stereotactic navigation is needed to prevent unnecessary complications, such as vertebral artery and neural injury.¹⁰⁸ When these precautions are taken, however, complication rates are quite low.^{98,103,104,108} The C2 isthmus is smaller in children than in adults, and its dimensions should be measured during preoperative screw planning to ensure that it is of adequate size to accommodate instrumentation. Screw trajectories should be simulated on stereotactic software before surgery to ensure safe placement. It has been demonstrated that the vertebral artery anatomy may prevent safe transarticular screw placement in one isthmus in 11 to 20% of cases, and in both in 4 to 5% of cases.^{108–110} Additionally, if there is a poor reduction of C1–2 subluxation with a significant offset of the articulating facet surfaces, there is a correspondingly higher incidence of screw malposition.¹⁰⁹

Goel-Harms Constructs

To address the disadvantages of C1–2 transarticular screw placement—namely, the degree of technical difficulty and cases in which the anatomy precludes safe placement—Harms and Melcher reported on their modification of the Goel construct, employing posterior atlantoaxial fixation with bilateral C1 lateral mass and C2 pars screws linked by metallic rods.^{111,112} Further modification with one or more C2 translaminar screws in place of pars screws is also possible. Another advantage of these constructs is that they can be used when a nonreducible C1–2 subluxation precludes transarticular screw placement. As with transarticular screw fixation, the concomitant use of wire and structural graft techniques is not required but may enhance immediate stability in flexion-extension and provide additional surfaces for osseous fusion. Preoperative screw planning should be undertaken in children to ensure that their anatomy will accommodate the available instrumentation, and screws should be placed under intraoperative fluoroscopic guidance.

Odontoid Screws

Type II odontoid fractures with an intact transverse ligament may be amenable to fixation via odontoid screw placement if

there is no excessive angulation or distraction of the fracture. An advantage of odontoid screw fixation over C1–2 transarticular screw placement for type II odontoid fractures is the preservation of physiologic motion at the C1–2 joint.

60.7.3 Subaxial Spine Instrumentation Sublaminar Wiring

Sublaminar wiring techniques in the subaxial spine involve the use of soft braided titanium cables or Mersilene (Ethicon, Somerville, NJ) tape that is looped bilaterally around adjacent laminae with structural bone grafts (i.e., autologous iliac crest) wired to the fusion surface.²⁹ Sublaminar wiring with structural graft techniques results in high fusion rates in children and has been shown to afford more stability than either interfacet or interspinous wiring.¹¹³ Care must be taken to prevent cortical violation of the laminae during dissection to reduce the incidence of the cables cutting into, or through, the bone.

Posterior Instrumented Fusion

In recent years, as a result of advances in surgical technique and instrumentation technology using lateral mass screws, pedicle screws, and derotating systems, posterior instrumented fusion of the pediatric spine has become commonplace. Posterior instrumentation allows decompression, reduction, and stabilization over a large number of segments, if required. Anterior instrumentation and fusion strategies are still used in specific circumstances but are much less common than posterior approaches. The main difficulties of instrumented fusion in children compared with that in adults include: whether a given patient's anatomy can accommodate the required instrumentation and withstand the stress applied by the construct, a smaller amount of bone surface for definitive fusion to occur, and the potential for alterations to spinal growth in young patients.

60.8 Conclusion

Spinal column trauma in the pediatric age group can result in neurologic deficit or spinal deformity. The injury level, pattern, and resulting stability are all heavily influenced by the unique anatomical characteristics and biomechanics of the developing spine. The prompt and accurate diagnosis of vertebral column injuries in children can be challenging because of an inability of young patients to accurately communicate, the unique radiographic appearance of the developing spinal column, and the inherent elasticity and recoil of the pediatric spine that may mask potentially unstable ligamentous injuries. The cervical spine, particularly the CVJ, is the most commonly injured region of the spine in children. Younger patients tend to have injuries at higher levels compared with older patients. Additionally, spinal column injuries in young children are more likely to be ligamentous, emphasizing the importance of dynamic imaging in properly obtaining a diagnosis. Fractures become more prevalent in older children and adolescents.

The majority of spinal column injuries in children ultimately do not require surgical intervention. Most are able to heal with external immobilization alone. Important considerations in the development of a treatment plan include the injury pattern and

stability, the neurologic status of the patient, the reducibility of the injury, the presence of compressive lesions, the likelihood of healing with external immobilization, and the degree of patient compliance with the treatment. Primary indications for surgical intervention include neurologic deficit from a compressive lesion or evidence of spinal column instability. Goals of surgery are neural decompression, reduction, and stabilization of the vertebral column. Advances in surgical technique and instrumentation technology continue to increase the options for operative intervention in children after spinal column trauma.

Pearls

- The injury level, pattern, and stability are directly influenced by the unique anatomical and biomechanical characteristics of the pediatric spinal column.
- The most important biomechanical principle in appropriate management of pediatric spinal column trauma is that of stability.
- The transition from an immature to a mature spine, in biomechanical terms, occurs at roughly 8 to 9 years of age.
- Spinal column trauma is more likely to result in ligamentous injury rather than fractures in young children; the older the child, the more likely that a given injury involves a fracture.
- Infants and young children are more likely than older children and adults to have injuries to the CVJ and upper cervical spine.
- In any child with a vertebral column injury, there should be a high suspicion for multiple contiguous and noncontiguous injuries.
- Dynamic imaging and MR imaging, when appropriate, are of particular importance in the diagnosis of pediatric spinal column trauma given the high incidence of purely ligamentous injuries.
- Distracting forces (e.g., traction) should be considered carefully in young children with cervical spine injuries given the high incidence of occipitocervical and atlantoaxial instability in this age group.
- The majority of spinal column injuries in children can be managed with external immobilization only.
- Surgical intervention is indicated for spinal column injuries resulting in neural compression or instability.
- Recent advances in surgical technique and instrumentation technology have increased the options available to neurosurgeons for the treatment of unstable spinal column injuries.
- The treatment of unstable injuries with rigid internal fixation and fusion often allows a reduction in the duration and intensity of external immobilization.

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61 Specific Injury Patterns and Treatment of Pediatric Spinal Column Trauma

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This chapter addresses the specific aspects of the diagnosis and appropriate management of the major classes of injury seen in pediatric spinal column trauma. Common presentations and the biomechanical implications associated with each injury type are discussed in the context of the unique anatomical characteristics specific to the immature spine. Although injury patterns throughout the entire developing spine are addressed, a particular emphasis is placed on craniovertebral junction (CVJ) and cervical spine injuries, as these are the most common within the pediatric population.

61.1 Specific Injury Types

61.1.1 Craniovertebral Junction Injuries

Atlanto-occipital Dislocation

Injury Description

Atlanto-occipital dislocation (AOD) involves traumatic separation of the occiput from C1 and is an injury primarily of the pediatric population, occurring more than twice as frequently in children as in adults (► Fig. 61.1 a–d). It is one of the most common fatal cervical spine injuries, resulting from high-energy acceleration–deceleration impacts, most often during motor vehicle accidents involving pedestrians. AOD is primarily a ligamentous injury; it is caused by either hyperextension or, less commonly, hyperflexion in combination with extreme rotation, lateral flexion, and distraction, which results in rupture of the O–C1 joint capsules and disruption of either or both of the tectorial membrane and alar ligaments.^{1–7} There are usually no fractures, although in older children and adolescents, stronger ligaments may result in avulsion fractures at the ligamentous attachments to the occipital condyles or the base of the clivus, as opposed to frank ligamentous rupture.^{3,4,6} There is often additional injury to the suboccipital and posterior cervical musculature and prevertebral intrafascial hemorrhage.

Clinical Presentation

Historically, AOD has been associated with a high incidence of at-the-scene mortality; however, increased resuscitation skills in the lay public, improved emergency medical service response times, better initial cervical spine immobilization, and more prompt diagnosis have led to an increasing number of survivors.^{8–13} Children with AOD generally present with cardiopulmonary failure and severe neurologic deficits resulting from supratentorial, brainstem, cranial nerve, and spinal cord injuries.^{14–18} Coma or severely altered mental status is common. Motor deficits in AOD vary depending on the level and degree of injury and range from subtle hemiparesis to flaccid quadriplegia. It is important to note that most survivors of AOD, including those with a severe initial presentation, such as flaccid quadriplegia, have incomplete injuries and ultimately may have a good outcome.

Radiographic Diagnosis

Radiographic findings on plain films may be subtle, and AOD should be suspected in any child involved in high-speed trauma, especially one presenting with cardiopulmonary instability and associated facial injuries. Because early diagnosis is paramount to mitigate additional neurologic injury, all patients with suspected AOD should undergo prompt initial radiographic screening with a lateral cervical spine plain film.

Historically, AOD has been classified according to the system developed by Traynelis et al in 1986, which defined three types based on the direction of displacement of the occiput with respect to the atlas: type I, with anterior dislocation; type II, with longitudinal dislocation; and type III, with posterior dislocation.¹⁹ The majority of children with traumatic AOD have a type I injury. Recently, use of the Traynelis classification system has largely been supplanted by use of the occipital condyle–C1 (O–C1) joint interval (CCI) of Pang et al for the diagnosis and classification of AOD (► Fig. 61.1a,b).^{20,21} A CCI of more than 4 mm in either the sagittal or coronal plane for one or both O–C1 joints is considered a positive finding. Alternatively, a Powers ratio of greater than 1 is always abnormal and is indicative of Traynelis type I AOD. A basion–axial interval of more than +12 mm is indicative of type I AOD, and a value of less than –4 mm represents type III AOD. The dens–basion (DB) distance of Wholey et al may also be used to assess for AOD, and values greater than 14 mm should be considered diagnostic.²²

Any patient with suspected AOD based on clinical presentation, compatible mechanism, or plain radiographic findings should undergo thin-cut computed tomography (CT) from the occiput to at least C2 with sagittal and coronal reconstructions. CT reconstructions through the O–C1 joint can more clearly demonstrate abnormal separation or translation of the articulation than plain films. However, it should be noted that if AOD is reduced at presentation, bony abnormalities may not be apparent on either plain films or CT scans.

AOD is commonly associated with other radiographic abnormalities on both CT and magnetic resonance (MR) imaging, including cervicomedullary subarachnoid hemorrhage, spinal cord injury (SCI) or compression, and traumatic brain injury (i.e., cerebral edema, contusions, traumatic subarachnoid hemorrhage, intraventricular hemorrhage, or diffuse axonal injury). MR imaging is useful when plain radiographs or CT is not diagnostic and may demonstrate disruption of the tectorial membrane or alar ligaments and hemorrhage or edema in the retropharyngeal and posterior soft tissues, as well as brainstem and spinal cord damage or compression (► Fig. 61.1c).

Treatment

The initial treatment for AOD begins in the field with aggressive cardiopulmonary resuscitation as needed. During resuscitation



Fig. 61.1 Atlanto-occipital dislocation. (a) Sagittal and (b) coronal reconstructed computed tomographic scans of the occipital condyle–C1 joint from a 4-year-old girl demonstrating an abnormally large occipital condyle–C1 joint interval (white arrowheads). (c) Sagittal fat-suppressed T2-weighted magnetic resonance image demonstrating associated spinal cord edema at the cervicomedullary junction and significant ligamentous injury. (d) Postoperative lateral radiograph from this patient demonstrating occipital condyle–C2 posterior fusion incorporating bilateral C1-2 transarticular screws.

efforts, the spine and head are temporarily immobilized in a neutral position, as discussed in Chapter 60 in the section on initial evaluation and treatment. In young children with a disproportionately large head-to-torso ratio, elevation of the

thorax with padding or blankets or the use of a specialized back board with a recess for the occiput prevents undue flexion of the neck and anterior dislocation. Immobilization with a rigid cervical collar should be maintained pending more definitive

treatment. If a properly fitting cervical collar is not available, the head of a young child may be temporarily immobilized by taping to the back board.

Following radiographic confirmation of AOD, if there is a reasonable chance of survival and meaningful neurologic recovery from associated supratentorial brain injuries, the child should undergo prompt external immobilization. AOD is exceedingly unstable, and the use of distracting cervical traction is contraindicated because it may result in additional cervicomedullary injury.^{23,24} Evolving brainstem findings following immobilization are suggestive of vertebral artery dissection.

Some authors have reported successful treatment and fibrous fusion in children with AOD by using only external immobilization in a halo vest.^{23,25–27} Others, however, have reported worsening neurologic deficits when internal stabilization was not pursued.⁹ Given that AOD is extremely unstable and there is a very real risk for delayed neurologic injury with inadequate immobilization, occipitocervical instrumentation and fusion should be strongly considered once the patient is medically stable and any associated brainstem swelling has begun to resolve, typically 5 to 7 days after injury. Because C1–2 instability cannot be independently elicited in the presence of AOD, longitudinal C1–2 instability should be assumed, and therefore internal fixation and fusion from the occiput to C2 is typically performed (► Fig. 61.1d).

Long-term stability is predicated on achieving bony arthrodesis across a wide area of the occipital bone and the posterior arches of both C1 and C2. Autologous structural bone graft, such as rib, iliac crest, or split calvarial bone, is the gold standard and is most commonly used. Given the high incidence of AOD in infants and very young children, the posterior elements may not be robust enough to accept internal fixation, although rigid internal fixation from the occiput to C2 has been reported in children as young as 18 months. If rigid internal fixation is not possible, then sublaminar fixation techniques with postoperative halo immobilization may be required to achieve adequate fusion rates.

Jefferson (C1) Fracture

Injury Description

First described by Sir Geoffrey Jefferson in 1920, fractures of the atlas (C1) result when axial compression is transmitted from the occipital condyles to the lateral masses of C1 (► Fig. 61.2).²⁸ Jefferson fractures are rare in children because the atlas is not completely ossified in this age group and the C1 ring contains a large amount of cartilage, allowing the dissipation of excessive axial loads.²⁹ The most common mechanisms of injury are falls and motor vehicle accidents. The posterior and neurocentral synchondroses of the atlas fuse at around 3 and 7 years of age, respectively.³⁰ In children, it is important to distinguish a Jefferson fracture from an unfused synchondrosis, which is generally not of any clinical significance.³¹ Alternatively, C1 fractures may occur through the synchondrosis and can be missed on plain radiographs.³⁰ Atlas fractures may be accompanied by disruption of the transverse ligament, resulting in atlantoaxial instability. There is a high incidence of associated C2 fracture.

Clinical Presentation

The classic presentation of a child with an atlas fracture includes neck pain, muscle spasm, decreased range of motion, and head tilt; the majority of patients have at least three of these four symptoms.²⁹ Neurologic deficit is rare because of the capacious size of the spinal canal at this level and the fact that pathologic axial loads result in widening of the C1 ring as it fractures.

Radiographic Diagnosis

The majority of atlas fractures can be diagnosed with plain radiographs or CT scans. CT has led to an increased recognition of these fractures in children (► Fig. 61.2a,b).³² On odontoid view radiographs, transverse ligament disruption is suggested if the sum of the total overhang of the C1 lateral masses on C2 is 7 mm or more (the “rule of Spence”). MR imaging can be used to further assess the integrity of the transverse ligament, if needed.

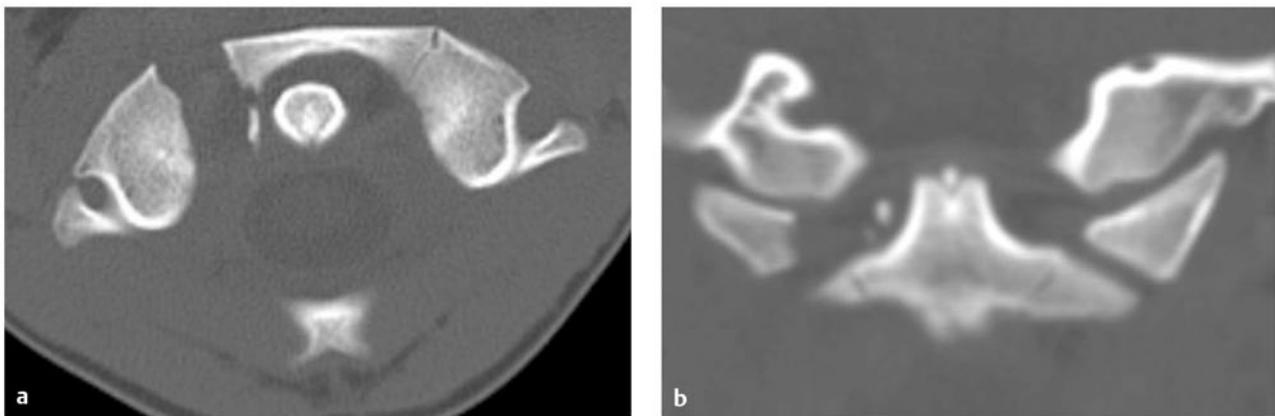


Fig. 61.2 Jefferson fracture. (a) Axial and (b) coronal computed tomographic (CT) scans demonstrating fracture through the right anterior arch and lateral mass of C1. If the sum of the total lateral overhang of the C1 lateral masses on C2 is ≥ 7 mm on odontoid view radiographs or coronal CT, then disruption of the transverse ligament should be suspected (the “rule of Spence”).¹¹⁹

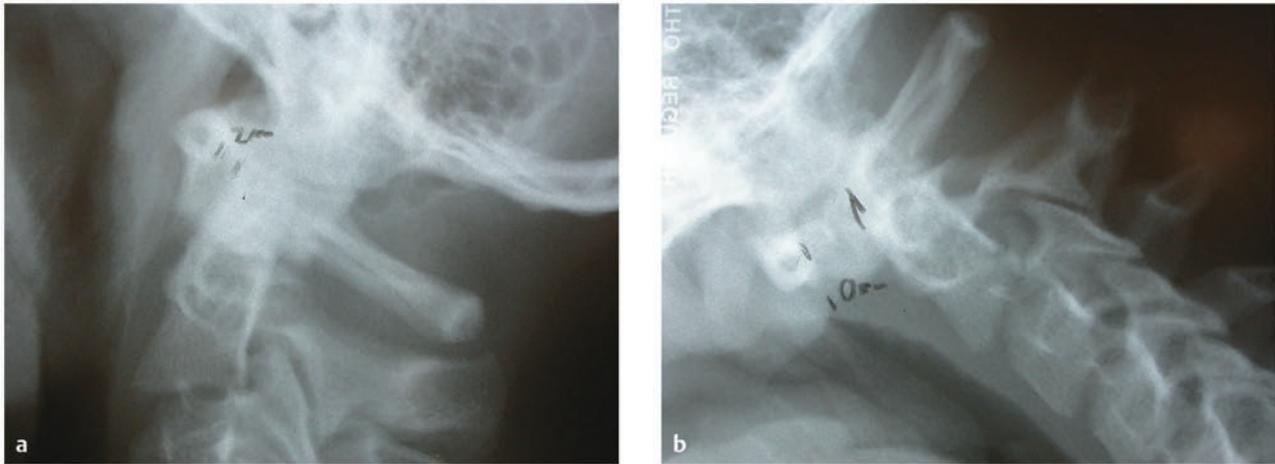


Fig. 61.3 Translational C1–2 subluxation. (a) Extension and (b) flexion radiographs demonstrating an atlantodental interval of 2 mm on extension and 10 mm on flexion, indicative of atlantoaxial instability in a 13-year-old boy following an assault to the head.

Treatment

The treatment of isolated Jefferson fractures with an intact transverse ligament is generally external immobilization in a rigid cervical collar, Minerva brace, or halo. If there is transverse ligament rupture and atlantoaxial instability, treatment should involve either halo immobilization or, rarely, C1–2 internal stabilization and fusion.

Translational Atlantoaxial Subluxation

Injury Description

Traumatic translational atlantoaxial (C1–2) subluxation is an extremely rare injury in children, often occurring as a result of a violent mechanism. There are few survivors (► Fig. 61.3, ► Fig. 61.4).^{33–36} The majority of affected children are 0 to 9 years old and often have purely ligamentous injury without fractures. In this age group, the dentocentral synchondrosis has less strength than the transverse ligament; therefore, epiphyseolysis of the odontoid process occurs more readily than transverse ligament rupture and translational C1–2 subluxation, partially accounting for the low incidence of this injury in children.³⁶ As such, traumatic translational atlantoaxial subluxation generally occurs under very specific circumstances and in the presence of predisposing factors. It is thought to result from disruption of the transverse ligament, allowing compression of the spinal cord between the odontoid process and posterior C1 arch. However, some autopsy studies have disputed this, reporting that injury to the C1–2 facet joints and capsules is more common than transverse ligament rupture in these patients.³⁴ A flexion mechanism is implicated in most cases of traumatic translational C1–2 subluxation³⁷ however, rare instances of posterior subluxation secondary to hyperextension or atlantoaxial distraction have been noted, even in the presence of a normal odontoid process and C1 ring.³⁸ Nontraumatic translational atlantoaxial subluxation is associated with developmental disorders that result in either laxity of the transverse ligament or odontoid hypoplasia (i.e., Down syndrome, Klippel-Feil syndrome, juvenile rheumatoid arthritis, Morquio syndrome, skeletal dysplasias).

Clinical Presentation

Like those with AOD, most children with traumatic translational C1–2 subluxation are victims of high-speed pedestrian–motor vehicle accidents.^{31,39,40} Patients frequently present at one of two extremes: with minor neck pain, C2 hypesthesia, and subtle myelopathy or with severe head injury and anoxic encephalopathy.⁴¹ Long-term survivors of traumatic translational C1–2 subluxation often have good neurologic outcomes, likely because of selected survival at the injury scene.

Radiographic Diagnosis

Translational atlantoaxial subluxation is most commonly diagnosed by an abnormally large atlantodental interval (ADI) on a lateral plain radiograph (► Fig. 61.3a,b). An ADI greater than 5 mm is considered abnormal in children younger than 8 years old, whereas 3 mm is the upper limit of normal in older children and adults.^{42–44} As the ADI exceeds 6 to 10 mm, the alar ligaments and tectorial membrane may become secondarily damaged and occipitoatlantal instability may ensue. The retropharyngeal soft tissues are usually widened on lateral plain films. If open-mouth odontoid views are obtained, it may be possible to visualize an avulsed C1 tubercle where the transverse ligament inserts onto the anterior C1 arch.⁴⁵ MR imaging may demonstrate rupture of the transverse ligament, with blood products, swelling, or rarely discontinuity of the ligament.^{46,47} Surgical treatment should be considered in patients with Down syndrome and an ADI of 6 mm or greater because 20 to 30% of these children will experience neurologic deterioration over time if intervention is not pursued.^{48–51}

Treatment

Because traumatic atlantoaxial subluxation is primarily an extensive ligamentous injury, the generally accepted treatment is C1–2 internal fixation and fusion (► Fig. 61.4a–d).^{39,41,52} Postoperative immobilization in a halo vest is recommended if nonrigid fixation is used,⁴⁵ but it may be deferred if C1–2 transarticular screws or other rigid internal fixation is employed.⁵³

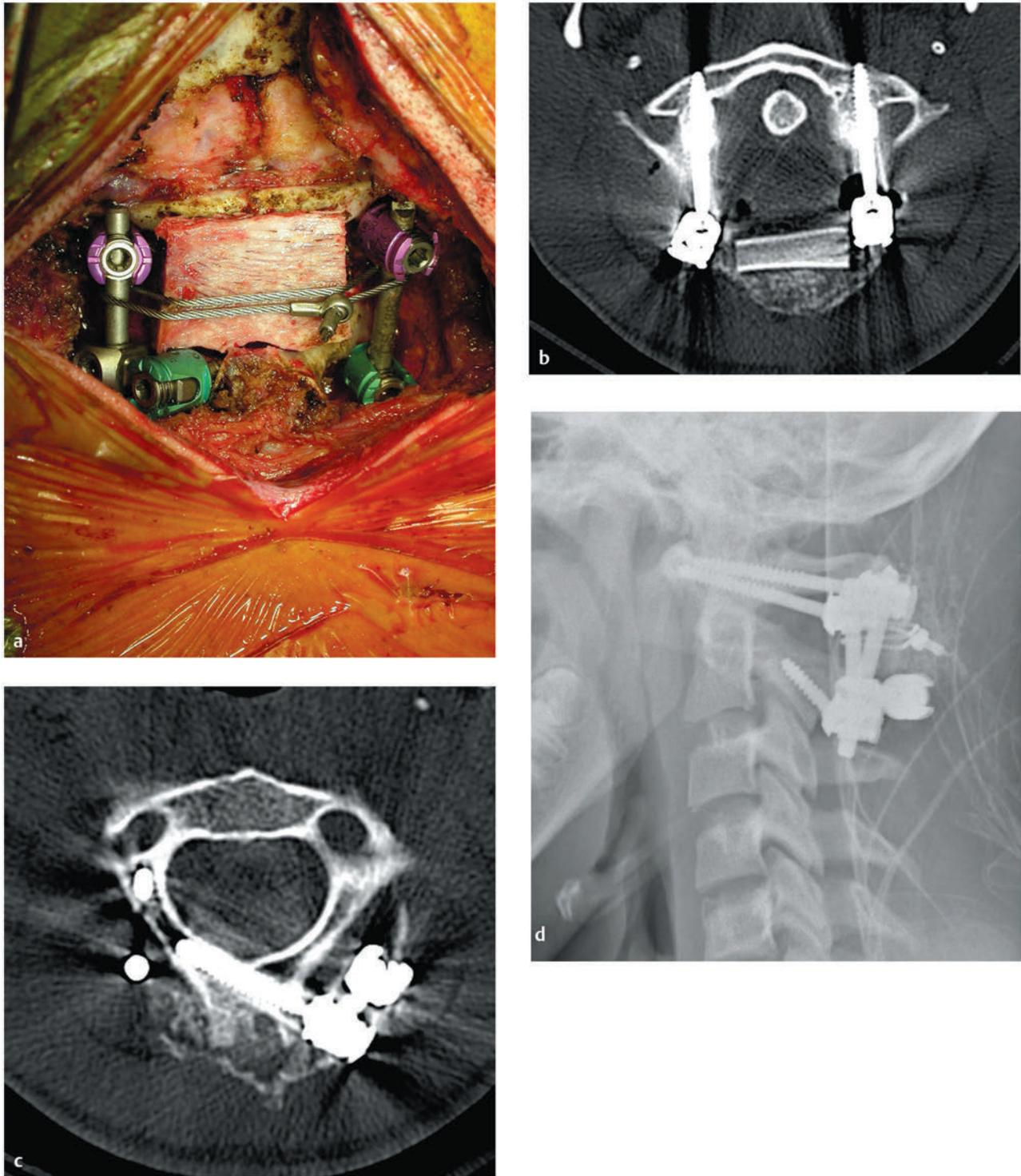


Fig. 61.4 Translational C1–2 subluxation. (a) Intraoperative photograph and (b,c) axial computed tomographic scans of a modified Goel-Harms type of fusion construct performed in the patient from ▶ Fig. 61.3 with traumatic C1–2 subluxation.^{63,64} Bilateral C1 lateral mass screws were placed and connected via metallic rods to the right C2 pars and left C2 laminar screws. An iliac crest bone graft was cabled in place between the posterior arch of C1 and the spinous process of C2. (d) Postoperative lateral radiograph of the fusion construct.

Atlantoaxial Rotatory Subluxation/ Atlantoaxial Rotatory Fixation

Injury Description

Atlantoaxial rotatory subluxation/atlas-odontoid fixation (AARS/AARF) represents a spectrum of abnormalities ranging from mild rotatory subluxation to absolute fixation with no motion (► Fig. 61.5, ► Fig. 61.6). Postulated mechanisms resulting in AARS/AARF include physiologic hypermobility of the C1–2 articulation, which can lead to rotatory subluxation during sudden and vigorous turning of the head, occasionally resulting in a true bony lock.³⁶ Other cases may be due to redundant synovial folds in children that become trapped in the C1–2 joint spaces at the extremes of rotation, jamming the articulation during counter-rotation; subsequent muscle spasm exacerbates the fixation.

Clinical Presentation

Only 30% of cases of AARS/AARF are traumatic in nature and usually result from only minor trauma.^{39,54} AARS/AARF has also been reported following inflammatory conditions of the head and neck, including pharyngitis, otitis media, retropharyngeal abscess (e.g., Grisel syndrome), and tumors.³⁸ Children with AARS/AARF classically present with neck pain and the neck maintained in lateral flexion with the chin rotated to the opposite side (“cock robin” deformity). The neck pain typically worsens with attempted rotation to the corrective side. Children with this injury usually have no neurologic deficits; however, patients may rarely present with C2 radiculopathy or myelopathy.⁵⁵ Although it has been reported, death directly attributable to AARS/AARF is exceedingly uncommon.³⁶

Radiographic Diagnosis

Plain radiographs and static CT are generally unreliable for the diagnosis of AARS/AARF and have been supplanted by dynamic (“three-position”) CT studies (► Fig. 61.5a,b). Nonetheless, complete cervical radiographs with flexion–extension studies should still be obtained in children with suspected AARS/AARF to rule out fractures and gross instability. Before the advent of CT, the Sudeck sign (deviation of the C2 spinous process toward the side of the chin tilt caused by a conscious effort of the child to realign the frontal visual axis coupled with involuntary counter-rotation of the subaxial spine) seen on anteroposterior plain films was pathognomonic for AARS/AARF.³⁶ Based on plain films, Field and Hawkins devised a classification scheme for AARS/AARF.⁵⁵ Type I is rotatory fixation without anterior or posterior shift of the atlas; it is the most common type in children and is also the most stable because the transverse ligament remains intact. Type II is rotatory subluxation with anterior shift of the atlas more than 3 mm but less than 5 mm; this type involves compromise of the transverse ligament and is therefore considered more dangerous. Type III is similar to type II, however, there is greater anterior shift (>5 mm). Type IV is rare and usually fatal, involving rotatory fixation with posterior shift of the atlas.

The relationship of C1 to C2 can be well visualized on dynamic CT, and CT is more accurate than plain films in diagnosing AARS/AARF.^{38,56} Lee and Pang developed a specific CT protocol wherein images are obtained with the patient’s head in certain positions to develop a C1–2 motion curve; deviation from the normal motion curve is then used to diagnose and determine the specific subtype of AARS/AARF.⁵⁷ Based on their data, AARS/AARF can be classified into several types and subtypes. Type I is a true bony lock, with a fixed C1–2 angle as the head

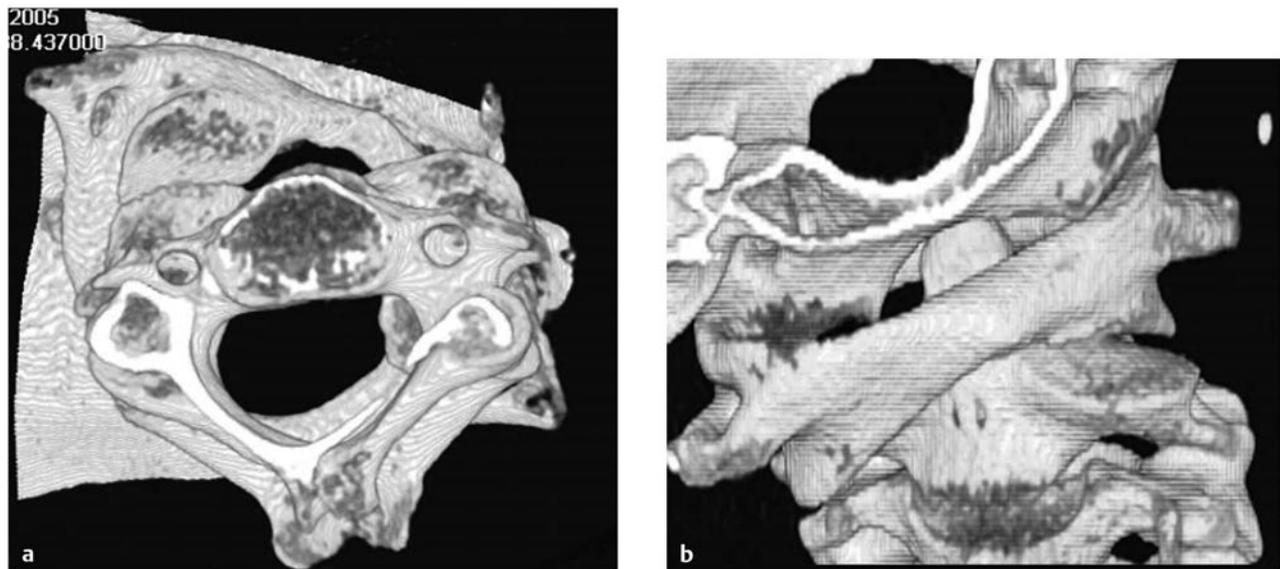


Fig. 61.5 Atlantoaxial rotatory subluxation (AARS). (a) Axial and (b) coronal three-dimensional reconstructed images of C1–2 in a 9-year-old girl with AARS that was refractory to conservative management. This patient ultimately required open reduction under general anesthesia with a posterior instrumented fusion.

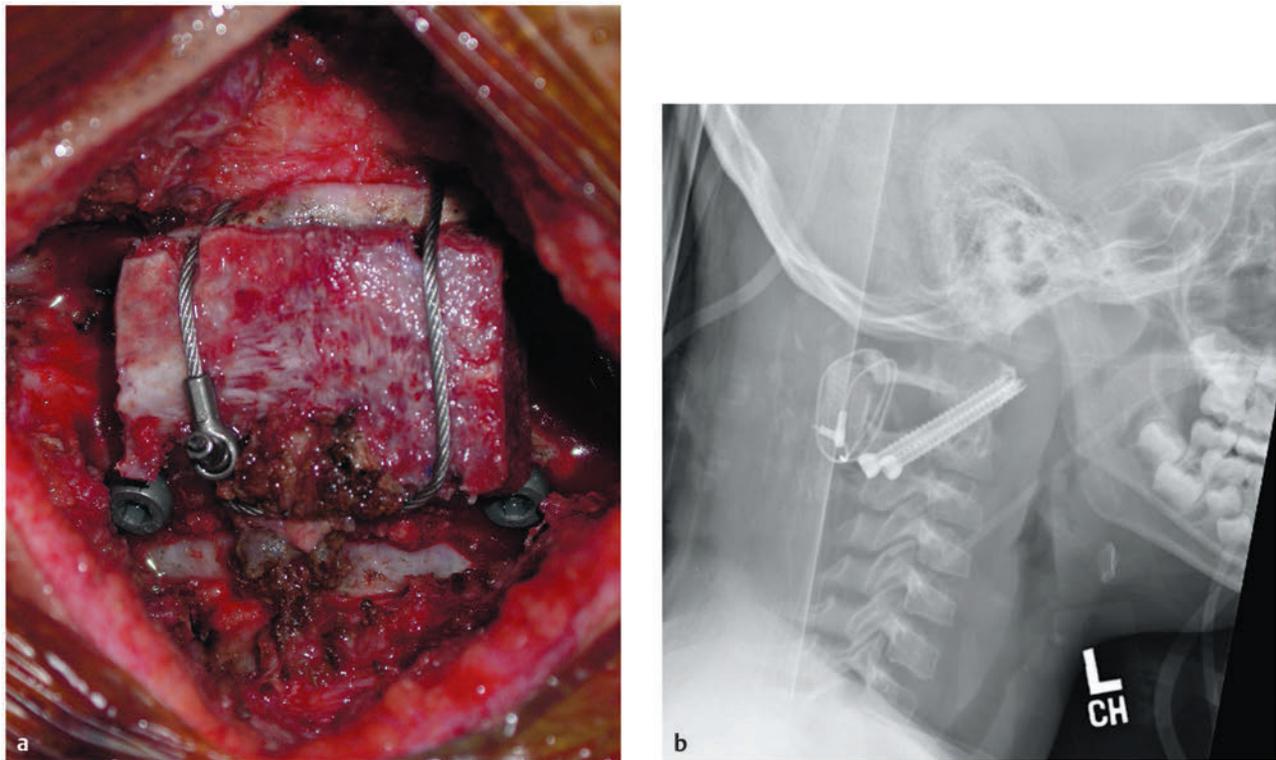


Fig. 61.6 Atlantoaxial rotatory subluxation (AARS). (a) Intraoperative photograph and (b) postoperative lateral radiograph of the fusion construct performed in the patient from ► Fig. 61.5 with refractory AARS. Following open reduction under general anesthesia, stabilization was achieved with bilateral C1–2 transarticular screws, and an iliac crest bone graft was cabled in Sonntag-Dickman fashion between the posterior arches of C1 and C2.⁶⁵

turns in the corrective direction. In type II, the C1–2 angle diminishes with corrective rotation; this type likely results from soft tissue interposition within the C1–2 joint, as opposed to a bony lock. Type II AARS/AARF is further subdivided into types IIA and IIB. In type IIA, the C1–2 angle never reaches 0 degrees because C1 never crosses to the other side of C2. This is the most common form of AARF. Conversely, in type IIB, C1 does cross to other side of C2, but only when C1 is at or less than 10 degrees. This suggests a pathologically sticky C1–2 articulation.

Treatment

The treatment of acute or subacute Field-Hawkins type I AARS/AARF generally consists of a combination of medical therapy (nonsteroidal anti-inflammatory drugs and muscle relaxants) and reduction via cervical traction.^{38,56,58} Following reduction, external immobilization for 4 to 6 weeks with a rigid collar is recommended. The duration of symptoms before treatment is a critical determinant of the response to conservative treatment. If treatment is not initiated within 1 month, the chances of restoring normal motion to the joint are much less than if treatment is begun acutely.³⁸ Recurrence of AARS/AARF should be treated with repeated reduction and halo immobilization. Failure of reduction or a second recurrence, which may indicate transverse ligament incompetence, should prompt consideration of open reduction and C1–2 fusion (► Fig. 61.6a,b).

Field-Hawkins types II and III should be considered inherently unstable because of injury to the transverse ligament and are most appropriately treated with open reduction and C1–2 fusion. Lee-Pang chronic type I (true bony lock) injuries are also unlikely to respond to conservative management. It is important to note that untreated atlantoaxial rotation can result in compensatory atlanto-occipital laxity and possible instability.^{38,59}

Odontoid Fractures

Injury Description

True odontoid fractures are rare in children (► Fig. 61.7). In children, translational C1–2 subluxation is most frequently the result of epiphysiolysis at the dentocentral synchondrosis, which is located slightly lower than the base of the dens within the rostral aspect of the C2 vertebral body and is not fused until 8 to 11 years of age. Most dentocentral synchondrosis fractures occur in children younger than 3 years of age.⁶⁰ These fractures tend to decompress the spinal cord and rarely lead to a neurologic deficit.

Clinical Presentation

The majority of children with fractures of the odontoid process present after severe falls or motor vehicle accidents, although

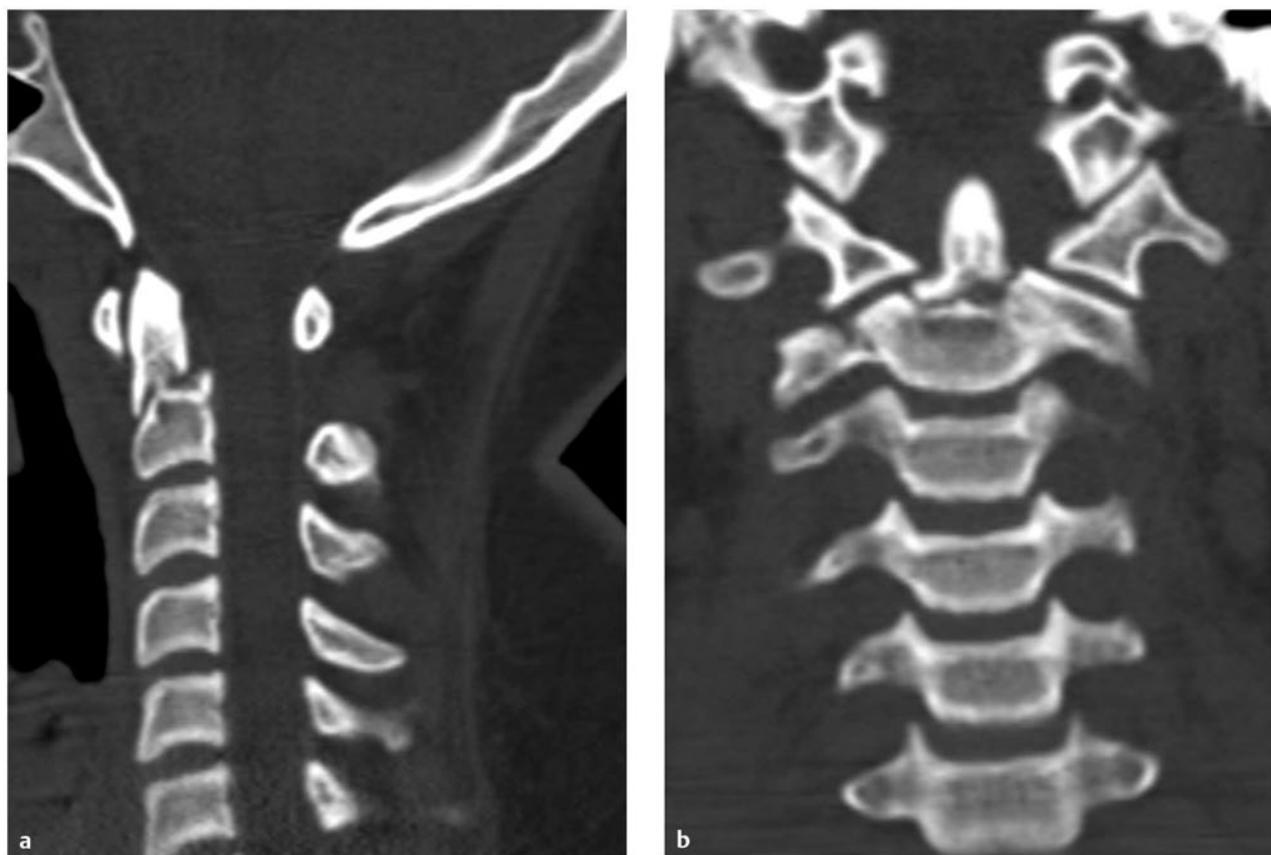


Fig. 61.7 Odontoid fracture. (a) Sagittal and (b) coronal computed tomographic scans demonstrating a type II odontoid fracture in an 18-year-old young man following a motor vehicle accident. Odontoid fractures in children are most commonly actually epiphysiolysis at the dentocentral synchondrosis (which is located slightly below the base of the dens in the rostral C2 body) rather than true odontoid fractures. The patient was successfully treated with halo ring immobilization.

some fractures may occur after only minor trauma. Neck pain is the most common complaint. Some patients may also be obtunded from concomitant head injury, given the high percentage of cervical injuries that are associated with head trauma.⁶¹ The majority of children who present with odontoid fractures are neurologically intact because cord injury at this level is often acutely fatal.

Radiographic Diagnosis

True odontoid or dentocentral synchondrosis fractures can easily be seen on lateral plain films. There is often anterior angulation or displacement of the rostral odontoid process (► Fig. 61.7a). The ADI is normal in isolated fractures. An abnormal ADI suggests concomitant disruption of the transverse ligament. In epiphysiolysis, CT may demonstrate an abnormally widened growth plate.

Treatment

There are few recommendations for the treatment of odontoid injuries in children. In a series of 35 children, Sherk et al reported that only 1 child with an odontoid injury required surgical fusion.⁴³ More recently, in a series of 13 children with odon-

toid fractures, 80% of those treated with halo immobilization for 10 to 18 weeks demonstrated a stable fusion. In general, children with odontoid fractures can be adequately treated with early external immobilization. C1–2 fusion is recommended in cases of failed fusion after immobilization or if the transverse ligament is disrupted.

Os Odontoideum

Injury Description

Os odontoideum was first described by Giacomini in 1886 and is a rare radiographic diagnosis defined as separation of an ossicle of bone from the odontoid process with no continuity to the body of the axis (► Fig. 61.8, ► Fig. 61.9, ► Fig. 61.10). Approximately 60% of patients present before 20 years of age, with a median age of 15 years. Although some authors have argued that os odontoideum is congenital, most now believe that it is an acquired lesion and represents a chronic nonunion from remote trauma. Functionally, os odontoideum is similar to a chronic type II odontoid process fracture, and most authors view it as unstable, with a risk for catastrophic injury to the upper cervical cord if left untreated.⁶²

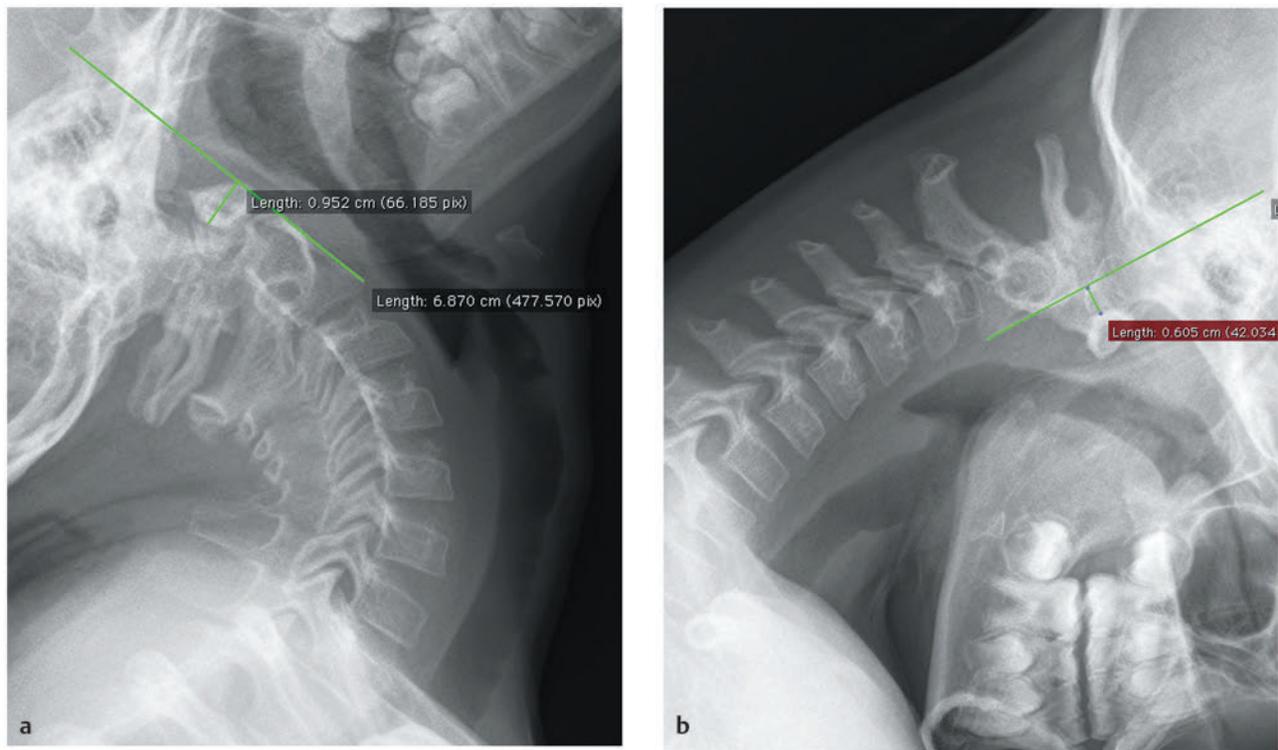


Fig. 61.8 Os odontoideum. Preoperative (a) extension and (b) flexion radiographs demonstrating gross instability with 15 mm of subluxation at C1–2 in a 9-year-old boy with os odontoideum who presented with vertebrobasilar insufficiency.

Clinical Presentation

The most common presenting symptom in patients with os odontoideum is neck pain, occurring in about two-thirds of patients. Approximately half of patients present following an instance of trauma, including falls, motor vehicle accidents, and sporting accidents. Neurologic symptoms on presentation may include myelopathy (23%) or transient paresthesias or quadriplegia (19%) following even relatively minor trauma.⁶² Headaches and symptoms suggestive of posterior circulation ischemia have also been reported (► Fig. 61.9c).

Radiographic Diagnosis

Os odontoideum can be diagnosed on lateral plain radiographs or CT scans demonstrating a well-corticated discontinuity between the odontoid peg and the body of the axis (► Fig. 61.8, ► Fig. 61.9, ► Fig. 61.10). The appearance is similar to that of a chronic type II odontoid fracture. The majority of patients demonstrate evidence of instability on flexion–extension radiographs (► Fig. 61.8a,b).⁶² MR imaging may demonstrate spinal cord edema in the C1–2 region.

Treatment

Most authors view os odontoideum as an unstable lesion with the potential for catastrophic cervical SCI from relatively minor

trauma even in asymptomatic patients. Treatment should include decompression (if necessary), reduction, and internal stabilization and fusion (► Fig. 61.10).⁶² This may be achieved through the use of transarticular screws or other C1–2 instrumentation (i.e., a Goel-Harms construct^{63,64}) in conjunction with a structural bone graft secured with cabling (e.g., the Dickman-Sonntag technique).⁶⁵

Hangman's (C2 Pars) Fracture

Injury Description

Hangman's fractures are rare in the pediatric population (► Fig. 61.11a–c). When a hangman's fracture does occur, it is most often due to a hyperextension mechanism, similar to that seen in adults. Classic causes include motor vehicle accidents, falls, diving accidents, and collisions during contact sports.

Clinical Presentation

Most children with C2 pars fractures present with neck pain. This fracture type typically results in widening of the spinal canal; therefore, neurologic deficits following a hangman's fracture are rare. Only a few cases of neurologic injury following this injury have been reported in children.^{66,67}

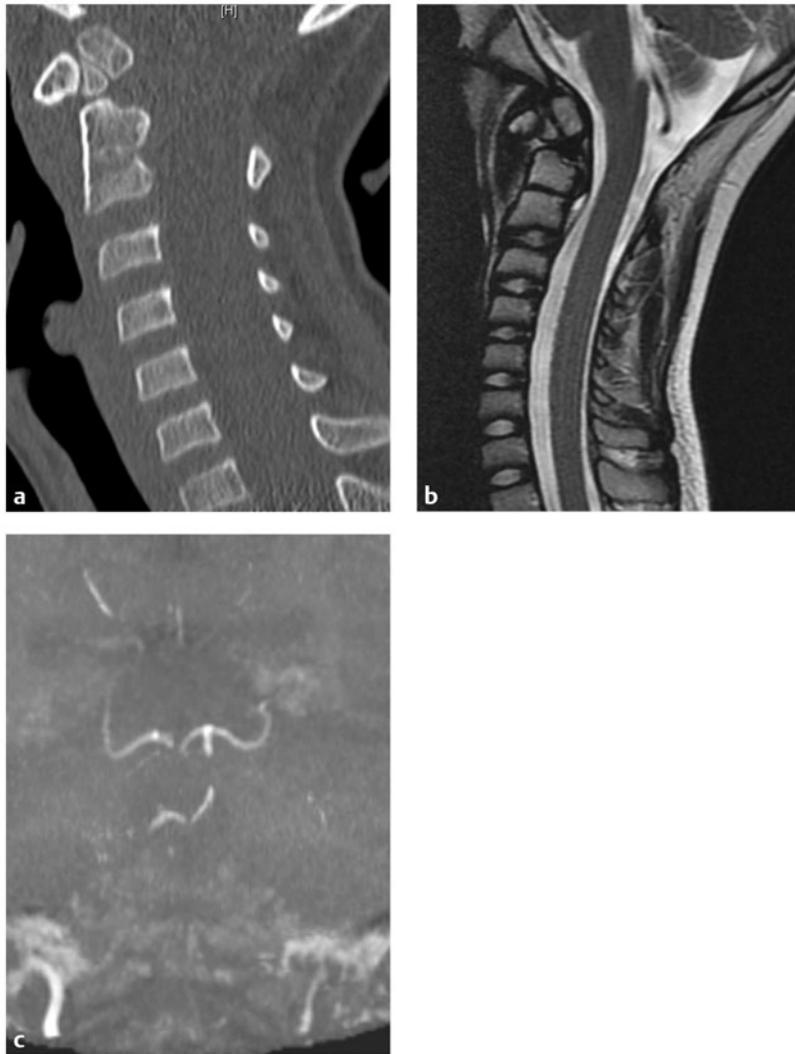


Fig. 61.9 Os odontoideum. Preoperative (a) sagittal computed tomographic and (b) sagittal magnetic resonance (MR) imaging of the same patient as in ▶ Fig. 61.8 clearly shows a well-corticated ossicle in the region of the dens in discontinuity with the remainder of the axis. (c) Preoperative MR angiogram from this patient demonstrating severe vertebral artery insufficiency from kinking of the vertebral arteries due to C1–2 instability.

Radiographic Diagnosis

The diagnosis of a hangman's fracture can be difficult in children because the neurocentral synchondrosis—the junction of the ventral and paired posterior ossification centers of the axis body—can mimic a fracture on oblique radiographs in patients younger than 7 years. Pseudo-subluxation at C2–3 may also be present in many children and can mimic true subluxation. When the diagnosis is in doubt on plain films, CT scans should be obtained through the region of interest.

Treatment

The treatment of C2 pars fractures is similar to that in adults.⁶⁸ If the body of the atlas is not significantly displaced on C3, immobilization in a rigid collar should be adequate. If there is anterior displacement greater than 3 mm, external immobilization in a halo vest or Minerva cast is more appropriate. Surgical fusion is rarely required and is generally reserved for cases in which external immobilization fails to result in healing of the fracture or in which there is evidence of significant associated ligamentous injury.

61.1.2 Subaxial Cervical Spine Injuries

Purely Ligamentous Injury (Subluxation without Fracture)

Injury Description

These injuries include trauma to the supporting ligaments and soft-tissue structures of the cervical spine below C2. They range from very mild to severe injuries that completely disrupt supporting structures, leading to gross spinal instability.

Clinical Presentation

Nearly all patients with purely ligamentous injuries of the subaxial cervical spine present with neck pain. Neurologic deficits, including radiculopathy, myelopathy, or both, may also be seen. Neck pain that persists for several weeks following trauma is unusual and should be investigated with radiologic studies.

Radiographic Diagnosis

Plain radiographs in a child with purely ligamentous injury of the subaxial cervical spine may range from normal to grossly



Fig. 61.10 Os odontoideum. Postoperative lateral radiograph of the fusion construct performed on the patient in ► Fig. 61.8 and ► Fig. 61.9. Following open reduction, stabilization was achieved with a Goel-Harms type of fusion construct,^{63,64} with bilateral C1 lateral mass and C2 pars screws and cabling of an iliac crest structural bone graft.

abnormal in appearance. Although static plain films may be normal, dynamic radiographs may unmask instability. The diagnostic criteria for determining instability in children with purely ligamentous injuries of the lower cervical spine are not well defined. White and Panjabi demonstrated that horizontal displacement of one vertebral body on another of more than 3.5 mm is consistent with significant ligamentous rupture in adults.^{42,69,70} The pediatric spine exhibits greater physiologic movement in the horizontal plane than does the adult spine. As such, displacement of up to 4.5 mm at a given segmental level may be considered normal and is termed *pseudosubluxation*, most commonly seen at C2–3 and C3–4.^{71,72} The following recommendations were developed by Pang and Sun to distinguish clinical instability from physiologic hypermobility in the subaxial cervical spine of children following trauma³⁶:

1. In children older than 8 to 9 years, the spine is developmentally similar to that of adults. Therefore, horizontal displacement of more than 3.5 mm should be considered unstable.
2. In children younger than 8 to 9 years, the physiologic mobility of the subaxial cervical spine is increased, particularly at C2–3 and C3–4. Horizontal displacement of more than 4.5 mm should be considered unstable.
3. In children younger than 8 to 9 years, if displacement between 3.5 to 4.5 mm is accompanied by prolonged muscle spasm, pain, neurologic findings, or other abnormalities (i.e., an avulsed spinous process or widened interspinous space), then clinical instability should be assumed.

In addition to horizontal displacement, the degree of kyphotic angulation following trauma can be used to determine whether a given injury is stable. White and Panjabi determined that the angle between adjacent vertebrae in normal adults is always less than 11 degrees and that kyphotic deformities with a larger angle should be considered unstable.^{42,69,70} In children, however, the developing spine is more elastic and predisposed to recoil. Therefore, following trauma, the angle of displacement demonstrated on lateral X-rays or CT may be much less than the maximal excursion at the time of impact, and a high degree of ligamentous disruption may accompany a minor kyphotic deformity on imaging. Most authors agree that a kyphotic angulation of more than 7 degrees likely represents a significant ligamentous injury that may predispose the developing spine to further kyphosis and instability.⁷³ Pang and Sun established the following algorithm to guide management in children with angular deformities of the subaxial cervical spine following trauma³⁶:

1. If a neutral lateral radiograph demonstrates more than 11 degrees of angulation, with or without neurologic deficits, overt instability should be assumed. Dynamic imaging should be deferred and surgical fusion considered.
2. If a neutral lateral radiograph shows between 7 and 11 degrees of angulation and there is a neurologic deficit, the injury is considered unstable. The assumption is that the displacement during the moment of impact must have been larger than that currently observed on imaging to result in myelopathy. Dynamic imaging should be deferred and surgical fusion considered.
3. If a neutral lateral radiograph demonstrates between 7 and 11 degrees of angulation and there is no neurologic deficit, then dynamic imaging should be obtained. If the angulation increases to 11 degrees or more, the injury is considered unstable and surgical fusion is appropriate. If the angulation is unchanged, dynamic imaging may be repeated in several days to eliminate confounding from muscle spasm. If repeated imaging demonstrates less than 11 degrees of angulation and the study is satisfactory, then external immobilization should be pursued until dynamic radiographs confirm healing of ligamentous structures.
4. If initial angulation on a neutral lateral radiograph is less than 7 degrees but the patient has severe pain and muscle spasm, external immobilization (i.e., a hard cervical collar) should be considered until satisfactory dynamic studies can be obtained to rule out instability.

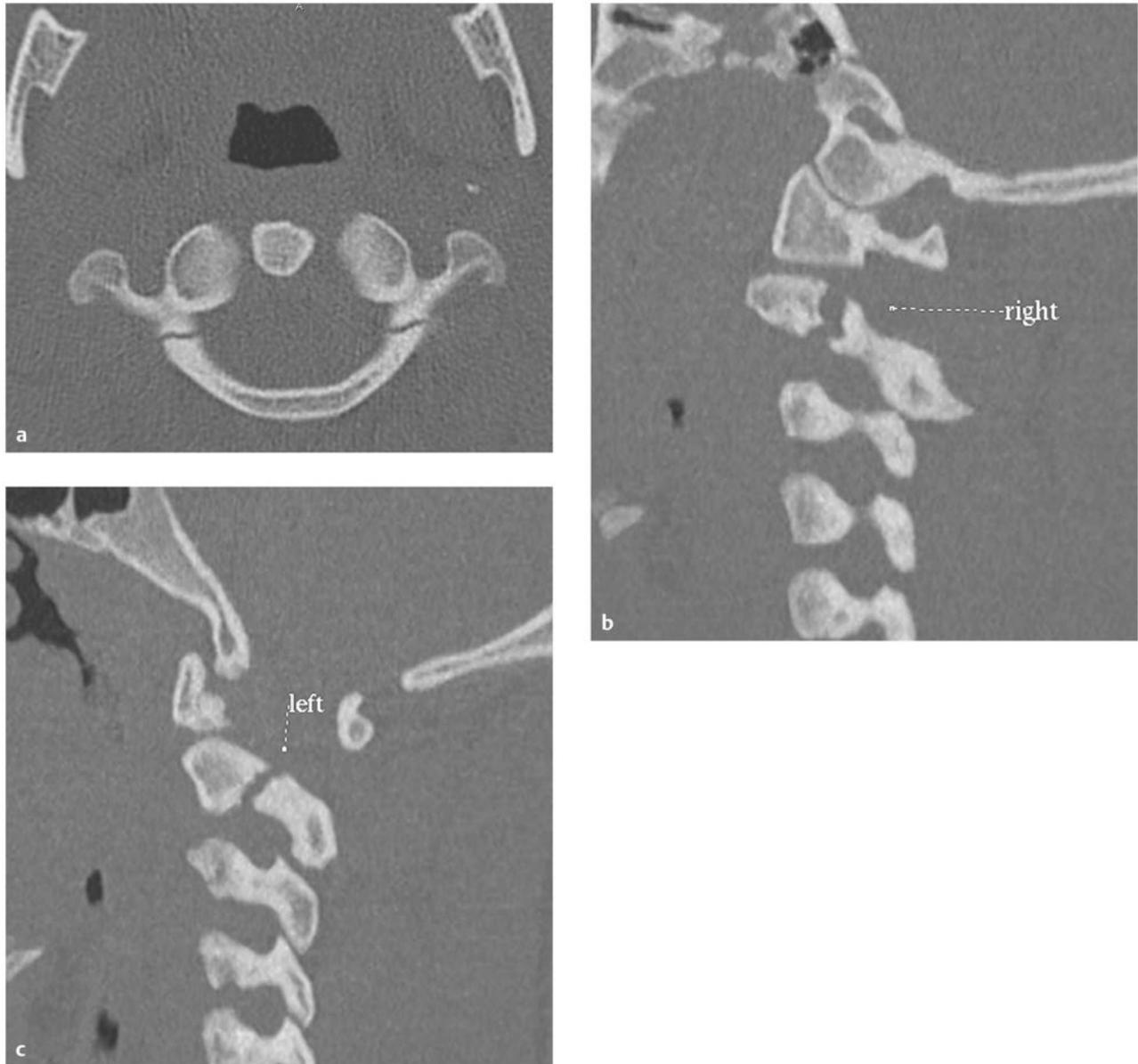


Fig. 61.11 Hangman's (C2 pars) fracture. (a) Axial and (b,c) parasagittal computed tomographic scans demonstrating a classic hangman's fracture with bilateral C2 pars involvement. Most fractures of this type can be treated with a rigid cervical collar if there is minimal displacement of the C2 vertebral body on C3. If there is more than 3 mm of displacement, external immobilization with a halo or Minerva brace should be strongly considered.

Evidence of instability in children with purely ligamentous injury of the subaxial cervical spine is often confined to a single level but may span two or more if the instability is particularly severe. CT scans are useful for confirming normal osseous anatomy and may also demonstrate indirect evidence of ligamentous injury, such as subluxation. MR imaging can be helpful to directly detect blood products in disrupted disk spaces or ligaments. On fat-suppressed T2-weighted MR imaging sequences obtained within 48 hours of trauma, high signal within the posterior interspinous and paraspinal soft tissues is suggestive of edema resulting from ligamentous and soft-tissue injury.

Treatment

Purely ligamentous injuries of the subaxial cervical spine that do not demonstrate gross instability on radiographic imaging can be managed conservatively with oral analgesics and, if necessary, a soft cervical orthosis for comfort. Most pain is associated with muscle spasm that usually resolves within 1 to 2 weeks after the injury. In children with more extensive ligamentous or soft-tissue injury that results in instability, operative reduction, internal fixation, and fusion should be considered. There are few series reporting on the management of purely ligamentous subaxial cervical spine injuries in children.

Finch and Barnes used primary operative stabilization to treat most children with this injury; however, they suggested that in at least some cases, external immobilization might have been sufficient.⁷⁴ Meanwhile, Pennecot et al treated minor ligamentous injuries with closed reduction and collar immobilization.⁷⁵ Despite this, however, 8 of 11 children in their series had injuries that ultimately required fusion. When operative management is undertaken, the operation to be performed depends on the specific pathology, as well as on surgeon and patient preference. Options include anterior approaches with allograft or autograft and plate/screw fixation, or posterior instrumented fusion. In cases of severe instability, instrumented fusion from combined anterior and posterior approaches may be considered to ensure proper alignment and long-term stability.

Osseous Anterior Column Injuries

Injury Description

Osseous anterior column injuries of the subaxial cervical spine (based on a two-column model) encompass all vertebral body

fractures from C3 to C7, including chip/teardrop, longitudinal, wedge compression, and burst fractures (► Fig. 61.12, ► Fig. 61.13). Fractures isolated to the anterior column are the most common fractures of the pediatric subaxial cervical spine.⁶⁰ The intervertebral disks of children have a higher collagen concentration, making them less predisposed to rupture when subjected to traumatic stresses. Instead, axial loading and compressive forces are transmitted to the annulus fibrosus and subsequently to adjacent vertebral bodies, which may then fracture. Burst fractures of the vertebral body may be categorized into one of five subtypes according to Denis: (1) type A, with both end plates involved; (2) type B, with only the superior end plate involved; (3) type C, with involvement of the inferior end plate only; (4) type D, which exhibits burst-rotation; and (5) type E, with burst-lateral flexion.⁷⁶

Clinical Presentation

Like those with other subaxial cervical injuries, most patients with osseous anterior column injuries present with neck pain. Some patients may be asymptomatic. The majority of these



Fig. 61.12 C7 burst fracture. (a) Sagittal computed tomographic scan and (b) magnetic resonance image demonstrating an unstable C7 burst fracture with spinal cord compression in a 17-year-old boy presenting with upper extremity paresthesias and numbness following a snowboarding accident. Also seen is a stable C5 anterior compression fracture with minimal angulation and loss of body height.

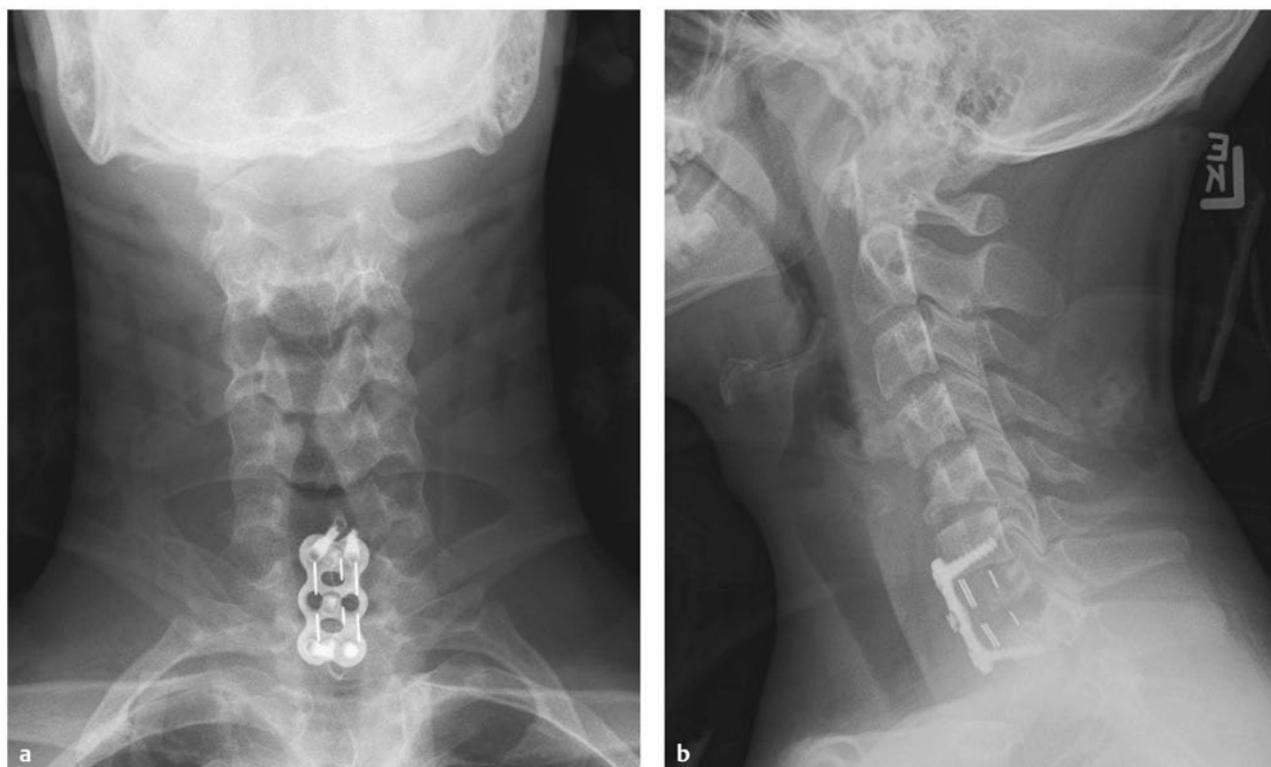


Fig. 61.13 C7 burst fracture. Postoperative (a) anteroposterior and (b) lateral radiographs of the patient in ▶ Fig. 61.12 demonstrating decompression via an anterior C7 corpectomy with placement of a synthetic interbody graft and anterior plating from C6 to C8.

injuries are discovered on screening lateral radiographs during the initial trauma evaluation when the patient reaches the hospital. If there is retropulsion of bone fragments into the spinal canal, patients may present with either myelopathy or radiculopathy. Higher cervical injuries, which are more frequent in the pediatric population, are more likely to result in injury to the spinal cord.

Radiographic Diagnosis

Most bony injuries to the anterior column of the subaxial cervical spine are visualized on plain radiographs. They may result in decreased vertebral body height, increased interpedicular distance, or splaying of the posterior facet joints. CT should be obtained if abnormalities on plain radiographs are not seen and suspicion for an injury is high (▶ Fig. 61.12a). MR imaging should be considered if the mechanism of injury is severe enough or the patient's examination is concerning for spinal cord or nerve root compression (▶ Fig. 61.12b). The utility of MRI has been demonstrated in identifying soft-tissue injury, acute disk herniation, and longitudinal ligament disruption, all of which may influence operative plans.⁷⁷ MR imaging is also valuable for detecting spinal cord contusions or infarctions in the presence of minor or remote fracture or in the absence of fracture.⁷⁸ In a study of high-risk patients with multiple injuries, plain films were 60% sensitive and 100% specific in detecting anterior column cervical injuries. CT was 90% sensitive and 100% specific in the same population.⁷⁹ This suggests the conclusion

that CT is valuable and should not be deferred in high-risk patients when subaxial cervical spine injury is suspected.

Treatment

The majority of osseous anterior column injuries in the subaxial cervical spine are stable fractures and heal in 4 to 6 weeks with conservative treatment. Immobilization with a rigid cervical collar is recommended for at least 2 to 4 weeks, with follow-up dynamic radiographs to confirm stability and rule out deformity.⁶⁰ Patients with significant kyphotic deformities or unstable injuries (burst fracture with spinal cord compromise and fractures associated with significant ligamentous disruption) should be managed surgically. For most significant osseous anterior column injuries the surgical treatment involves anterior cervical corpectomy and fusion with plating (▶ Fig. 61.13a,b).

Osseous Posterior Column Injuries

Injury Description

Injuries to the bony elements of the posterior column of the subaxial cervical spine encompass several types of fractures, including those to the facets, lateral masses, laminae, and spinous processes (clay shoveler's fracture). Also included in this category are jumped and perched facets, which may occur in conjunction with facet fractures. Isolated osseous posterior column injuries are rare in children and most often occur in

combination with ligamentous injury. Unilateral and bilateral facet dislocations have been reported in some series to be the second most common injury to the pediatric subaxial cervical spine.⁶⁰

Clinical Presentation

Posterior column injuries of the pediatric subaxial spine most often result from hyperextension, distraction, or rotation shear mechanisms.⁷⁶ Lamina and spinous process fractures are most often caused by hyperextension. Jumped and perched facets result from a combination flexion–distraction force, whereas rotation–compression forces tend to cause facet fractures.

The single most common presenting symptom is neck pain. Unilateral facet injury should be suspected when neck pain is accompanied by an isolated nerve root finding. Radiculopathy and myelopathy are not uncommon sequelae of osseous posterior column injuries in children.

Radiographic Diagnosis

Plain radiographs are usually sufficient to diagnose jumped or perched facets and spinous process fractures. Subluxation of more than 50% of the vertebral body width on lateral plain radiographs is almost pathognomonic for bilateral jumped facets.⁶⁰ Other osseous posterior column injuries may be quite difficult to discern without the addition of CT. MR imaging is useful for determining the degree of associated ligamentous injury and evaluating for underlying SCI or compression. MRI should be obtained if a child presents with neurologic findings or if plain radiography or CT demonstrates evidence of instability.

Treatment

The appropriate treatment of osseous posterior column injuries of the subaxial cervical spine is guided by a determination of whether the injury is stable or unstable. Stable bony injuries may be treated with a cervical collar for comfort. For grossly unstable injuries, such as bilateral jumped facets, treatment should involve reduction and surgical fusion. If the patient is alert and has a reliable neurologic examination to be followed, closed reduction may be attempted manually or with tong traction. If closed reduction fails, open reduction during the fusion operation should be performed. Alternatively, one may forgo attempts at closed reduction and proceed directly to open reduction and fusion, particularly when an injury is subacute or chronic. In these cases, the presence of significant muscle spasm and taught ligaments often makes achieving a successful closed reduction unlikely. It is prudent to obtain an MRI study before reduction, if possible, to assess for an asymptomatic herniated intervertebral disk or impending spinal cord compression that may be exacerbated during reduction maneuvers.

For some injuries, the determination of stability is less clear. Examples include unilateral perched or jumped facets. If malalignment of the facets can be corrected with closed reduction, the injury may heal over time with external immobilization only. In these instances, it is critical to take into account the amount of associated ligamentous injury and whether the anterior column is additionally involved. If conservative treatment is pursued, flexion–extension radiographs should be

obtained 2 to 3 months following trauma to assess for maintenance of stability. Persistent neck pain despite appropriate reduction and external stabilization should raise the suspicion of significant concomitant ligamentous injury and argues for surgical fusion.

Combined Anterior and Posterior Column Injuries

Injury Description

Combined anterior and posterior column injuries involve disruption of all supporting structures (i.e., bone, ligaments, and soft tissues) of the subaxial cervical spine at one or more levels (► Fig. 61.14, ► Fig. 61.15). Fracture–dislocation injuries fall into this category. They are rare in the pediatric age group, result from severe trauma, and are highly unstable.

Clinical Presentation

Most children with combined anterior and posterior column injuries present following severe trauma with a high-energy mechanism. A large percentage of these patients have evidence of a neurologic deficit from SCI.⁶⁰

Radiographic Diagnosis

Because of disruption of all supporting elements of the spinal column, plain radiographs will typically demonstrate misalignment of the cervical spine with distraction of the interspace at the level of injury.⁶⁰ CT is helpful to delineate fractures associated with the injury complex (► Fig. 61.14a,b). MRI is useful in assessing the degree of ligamentous and soft-tissue injury, as well as in identifying compressive lesions (e.g., herniated fragments from intervertebral disk rupture) and SCI (► Fig. 61.14b).

Treatment

Combined anterior and posterior injuries, including fracture–dislocations, are inherently unstable and must undergo surgical stabilization. Either an anterior or posterior approach, or both, may accomplish this, as long as the primary goals of spinal cord decompression and sufficient spinal column stability are accomplished. The choice of which approach to pursue depends on the specific pathology of the injury (e.g., the presence of an anterior compressive lesion) and surgeon preference. Combined anterior and posterior fusion is recommended when gross instability is evident to prevent hardware failure and avoid the necessity of a postoperative halo orthosis (► Fig. 61.15a,b). Surgical treatment should be performed as soon as medically feasible following the injury, generally within the first several days.

61.1.3 Thoracic and Lumbar Spine Injuries

Traumatic injuries to the thoracic and lumbar spinal column in children are significantly less common than injuries to the cervical spine. In the United States, motor vehicle accidents are the most common cause of thoracic and lumbar spine

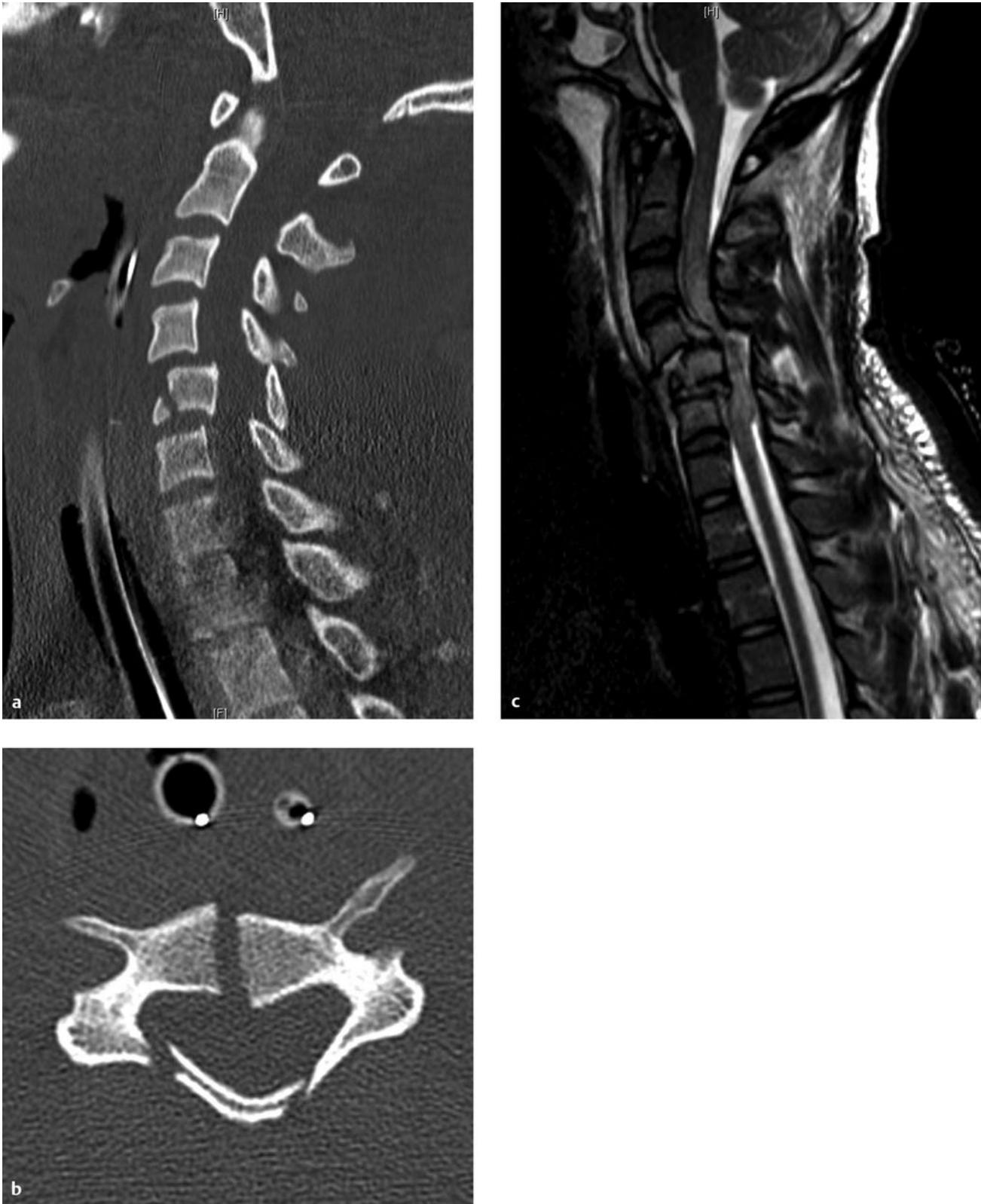


Fig. 61.14 Cervical fracture–dislocation. (a,b) Sagittal and axial computed tomographic scans and (c) sagittal magnetic resonance (MR) image of an 18-year-old boy with fracture–dislocation at C5 and a complete spinal cord injury following a motor vehicle accident. This injury involves disruption of the osseous and ligamentous structures of the anterior and posterior columns of the cervical spine, resulting in gross instability. Note the displacement of the C4 vertebral body on C5 and the jumped facets at the level of injury. The MR image demonstrates disruption of the anterior and posterior longitudinal ligaments and intervertebral disks, as well as extensive soft tissue and spinal cord edema. The patient was kept in cervical traction to maintain alignment until surgical decompression and stabilization were performed.

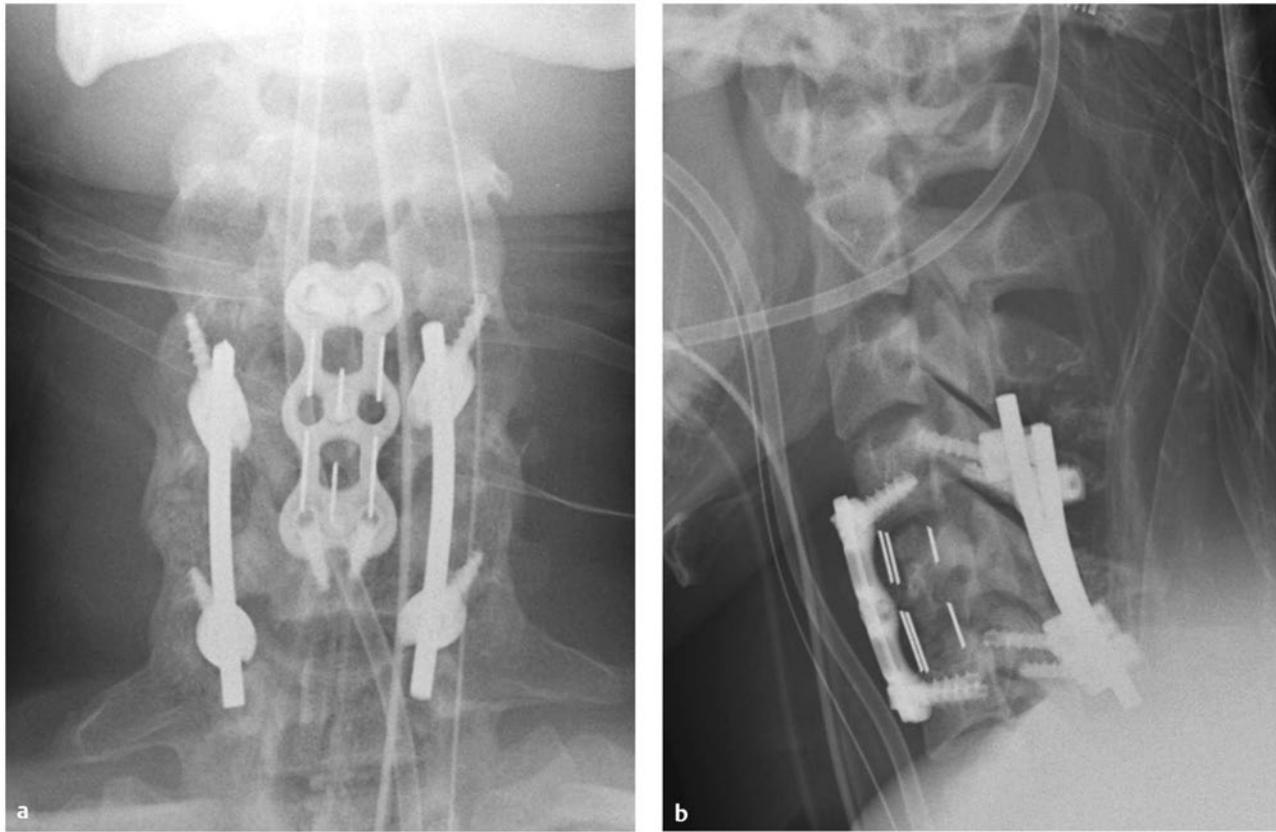


Fig. 61.15 Cervical fracture–dislocation. Postoperative (a) anteroposterior and (b) lateral radiographs of the patient in ▶ Fig. 61.14 demonstrating a combined anterior and posterior approach for decompression, reduction, and stabilization of his cervical fracture–dislocation. The initial stage consisted of a C5 corpectomy, reduction, placement of a synthetic interbody graft, and anterior plating from C4 to C6. This was followed by posterior segmental instrumentation and fusion from C4 to C6.

trauma in all pediatric age groups. Other common causes include pedestrian-versus-vehicle accidents and falls.⁸⁰ Similar injury types are commonly encountered in both the thoracic and lumbar spine in children, including compression (anterior or wedge) fractures, burst fractures, flexion–distraction injuries (Chance fractures), fracture–dislocation injuries, and apophyseal ring fractures.

Isolated thoracic spinal column trauma is quite rare because most flexion–extension within the spinal column occurs at the cervical and lumbar regions, making those regions more susceptible to injury. Osenbach and Menezes documented thoracic injury in only 13% of cases of children with spinal column injury or SCI without radiographic abnormality (SCIWORA),⁸¹ and Hadley et al reported that in a series of 122 children with spinal column trauma, only 11 (9%) had a purely thoracic spine injury.³¹ Thoracic spinal column injuries are most commonly compression or burst fractures. Mechanisms of injury include excessive axial loading and flexion forces from high-velocity impacts.

Lumbar spinal column injuries in children are most commonly caused by a flexion–extension mechanism and are frequently associated with lap seat belt use in the absence of a shoulder strap or harness. Flexion–distraction (Chance fracture), fracture–dislocation, and apophyseal injuries are the most common injury types in this region. Fractures are less

common in the lumbar spine than in the thoracic spine. When they do occur, older children are more likely to be affected.⁸²

Compression (Anterior Wedge) Fracture

Injury Description

Compression fractures of the anterior column are the most common type of fracture in the pediatric thoracic spine (▶ Fig. 61.16a,b). They are most frequently caused by a combination of flexion with axial loading and often affect multiple levels, occasionally with skipped, intervening normal levels.⁸³ Therefore, when one fracture is identified, additional compression fractures should be assumed to be present until it is proved otherwise. Like burst fractures, these fractures are more common in older children and adolescents.⁸⁴ Compression fractures are typically stable fractures because they involve only the anterior column (based on a three-column model of the thoracolumbar spine). The development of kyphosis or scoliosis in the year following a thoracic fracture is not uncommon; however, it is unclear whether the majority of these deformities are stable or increase in adulthood and become clinically relevant.⁸⁵ Persistent kyphotic deformity resulting from compression fractures is particularly uncommon in young children given continued bone growth and remodeling in this age group.⁸³

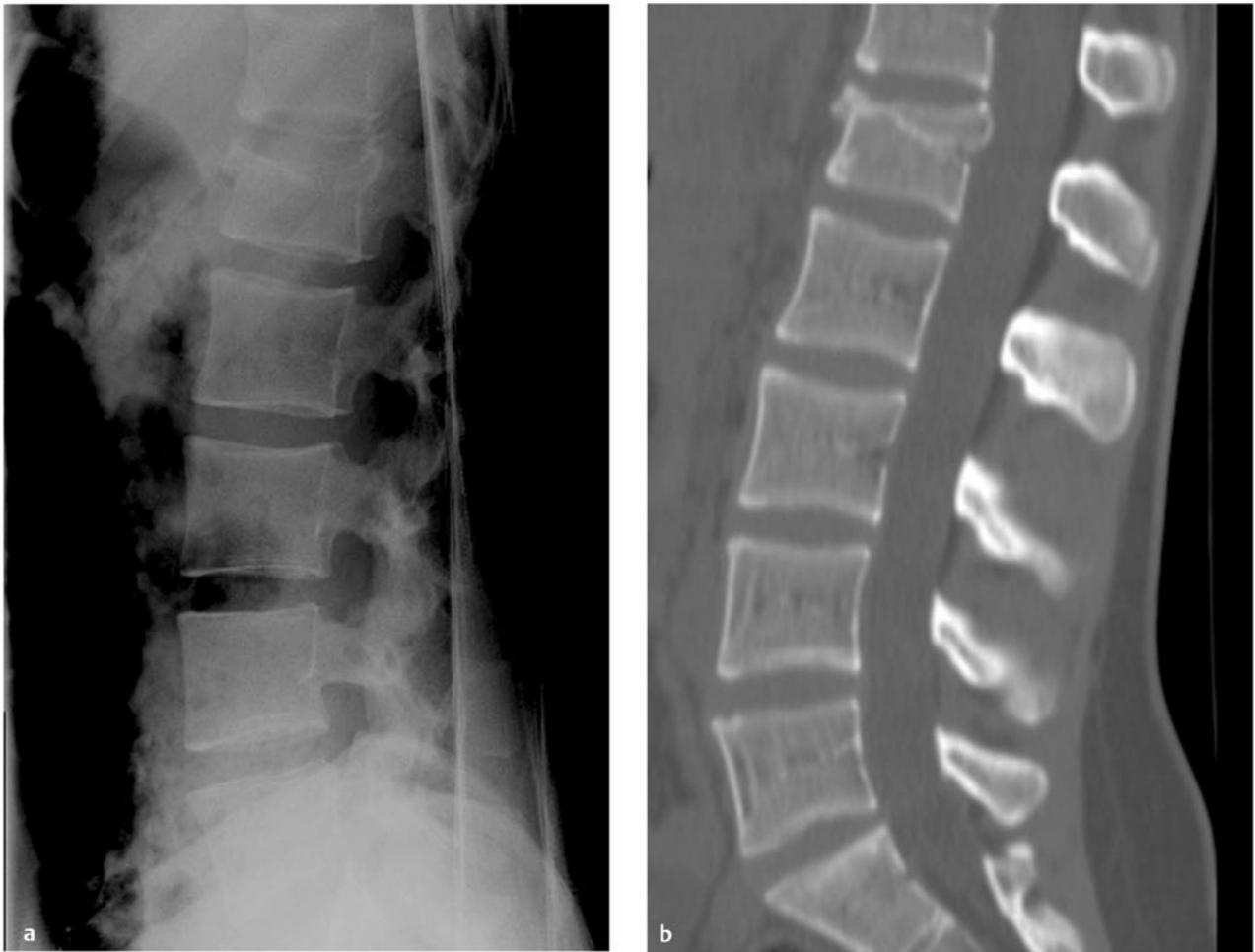


Fig. 61.16 L1 compression (anterior wedge) fracture. (a) Lateral radiograph and (b) sagittal computed tomographic scan demonstrating a nonoperative compression fracture of L1 in a neurologically intact young girl. Note the lack of significant angulation or retropulsed bone fragments. Thoracolumbar compression fractures can often be treated conservatively. External immobilization may aid in pain control and prevent the development of deformity during fracture healing and remodeling.

Clinical Presentation

The most common acute presentation of a child with a compression fracture of the thoracolumbar spine is localized axial back pain. Neurological deficit is rare given that only the anterior column is involved. Some children may present in a delayed fashion with pain or, less commonly, neurological deficit from progressive deformity.

Radiographic Diagnosis

The majority of thoracolumbar compression fractures can be adequately diagnosed and assessed with upright anteroposterior and lateral plain radiographs that demonstrate anterior wedging of the affected vertebral body (► Fig. 61.16a). Given the high incidence of multiple and skipped fractures, imaging of the entire spine should be routinely obtained when a compression

fracture is suspected. Kyphotic deformity may be present if multiple levels are affected. CT should be reserved for cases in which operative intervention is being considered. MRI should be performed in the exceedingly rare instance of an associated neurologic deficit.

Treatment

Because compression fractures of the anterior column of the thoracolumbar spine are stable injuries, the majority of patients should be treated conservatively with external immobilization in a thoracolumbar orthosis. Bracing may aid in pain control and prevent the development of kyphotic or scoliotic deformities during healing and remodeling of the fracture. Progressive kyphosis is more common in children with multiple compression fractures. In these children or others who develop significant deformities with persistent pain or neurologic deficit,

operative intervention, including instrumented fusion, may be appropriate.

Burst Fracture

Injury Description

Burst fractures of the thoracolumbar spine are caused by excessive axial loading and compromise of both the anterior and middle columns (► Fig. 61.17a–c). Like compression fractures, burst fractures are more common in older children and adolescents.⁸⁴ Retropulsion of bone fragments into the spinal canal may result in neurologic deficits. The risk for neurologic injury

has been shown to be more significantly associated with the level of injury than with the degree of canal compromise.⁸⁶ Thoracic burst fractures pose the greatest risk in this regard. Burst fractures may be either stable or unstable, generally depending on the degree of associated posterior ligamentous injury.

Clinical Presentation

Children and adolescents with thoracolumbar burst fractures most commonly present with localized axial back pain. Neurologic deficit, including radiculopathy from nerve root compression or myelopathy from cord compression, is much more

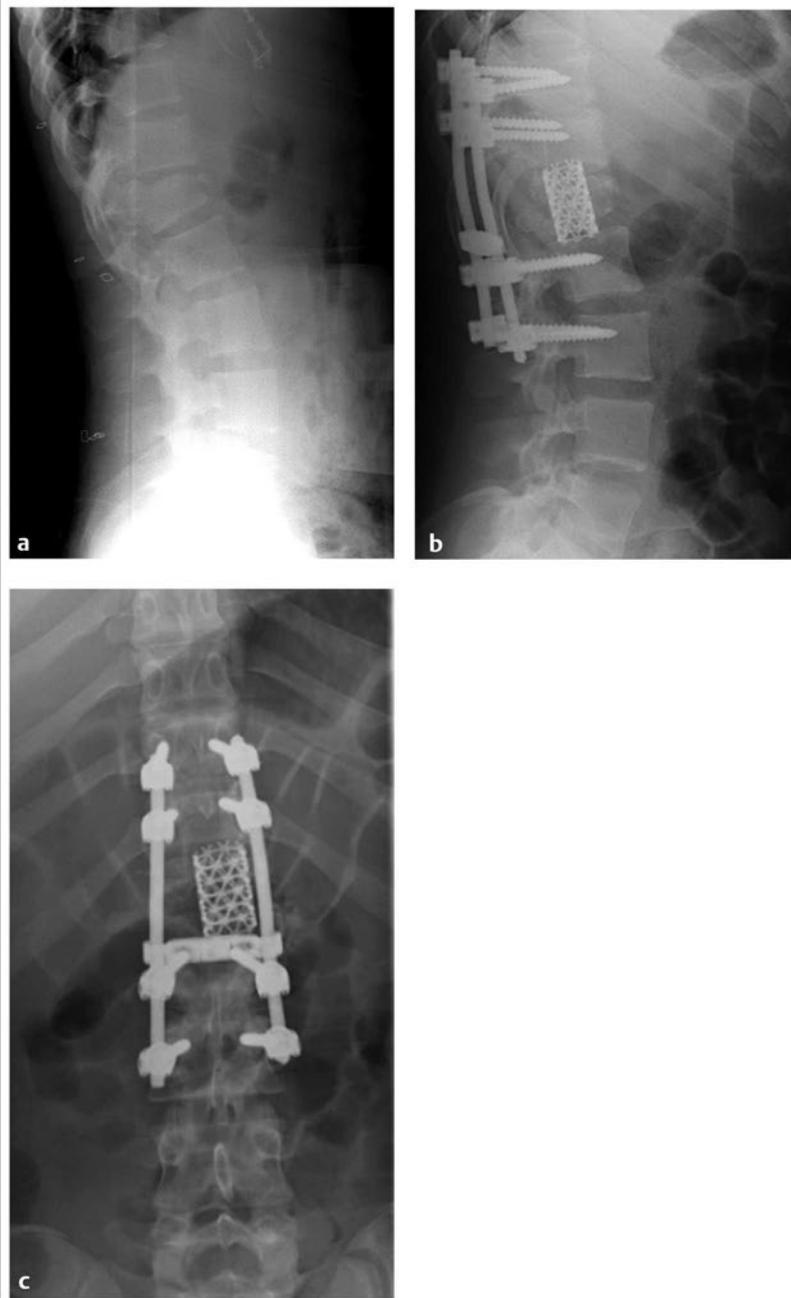


Fig. 61.17 L1 burst fracture. (a) Lateral radiograph demonstrating an unstable burst fracture of L1 in a 16-year-old girl who presented with an incomplete spinal cord injury following an all-terrain vehicle accident. The patient underwent decompression and stabilization through a posterior approach. Postoperative (b) lateral and (c) anteroposterior radiographs demonstrate an L1 corpectomy, placement of a metallic interbody cage, and placement of posterior segmental instrumentation and fusion from T11 to L3.

common than with compression fractures because of involvement of the posterior vertebral body and the potential for retro-pulsion of bone fragments into the spinal canal.

Radiographic Diagnosis

Plain anteroposterior and lateral radiographs are usually diagnostic for burst fractures, demonstrating involvement of both the anterior and middle columns of the thoracolumbar spine and associated loss of vertebral body height (► Fig. 61.18a). Retropulsed bone fragments may be observed. As with compression fractures, injury to multiple levels is not uncommon, and the entire spine should be screened with plain radiographs when a burst fracture is identified. CT is useful in these injuries to more accurately define the amount of vertebral body height loss, degree of kyphosis, and degree of canal compromise. MR imaging in the acute setting is valuable to further elucidate the degree of spinal cord or nerve root compression and assess the amount of associated posterior ligamentous injury, which aids in the differentiation between stable and unstable burst fractures.

Treatment

Children with no neurologic deficit and a stable burst fracture may be treated conservatively with external immobilization in a thoracolumbar orthosis. Children with unstable fractures or those with neurologic deficit from nerve root or cord

compression should undergo operative management. The goals of surgery should be decompression of the affected neural elements, fracture reduction, and stabilization of the spinal column.⁸⁷ Options include anterior decompression, posterior decompression, structural interbody graft placement, anterior fusion, posterior fusion, or a combination of the above, as determined by the expertise of the individual surgeon. Dorsal and dorsolateral approaches to the vertebral body (i.e., transpedicular, costotransversectomy, and lateral extracavitary approaches) may mitigate the risks associated with anterior approaches (► Fig. 61.17b,c). Few series have reported on the long-term outcomes of operative intervention in pediatric patients with thoracolumbar burst fractures. Lalonde et al. however, did publish a small series of 11 children with this injury; 6 patients were treated nonoperatively with external bracing, and 5 patients with more severe fractures underwent surgical stabilization.⁸⁸ In this series, the children who were treated surgically were less likely to develop long-term kyphotic progression than those who were treated nonoperatively.

Flexion–Distraction Injury (Chance Fracture)

Injury Description

Chance fractures most frequently occur in the upper lumbar region and involve a horizontal fracture through all three columns of the spine, including the vertebral body, pedicles, and laminae. These injuries are classically associated with the use

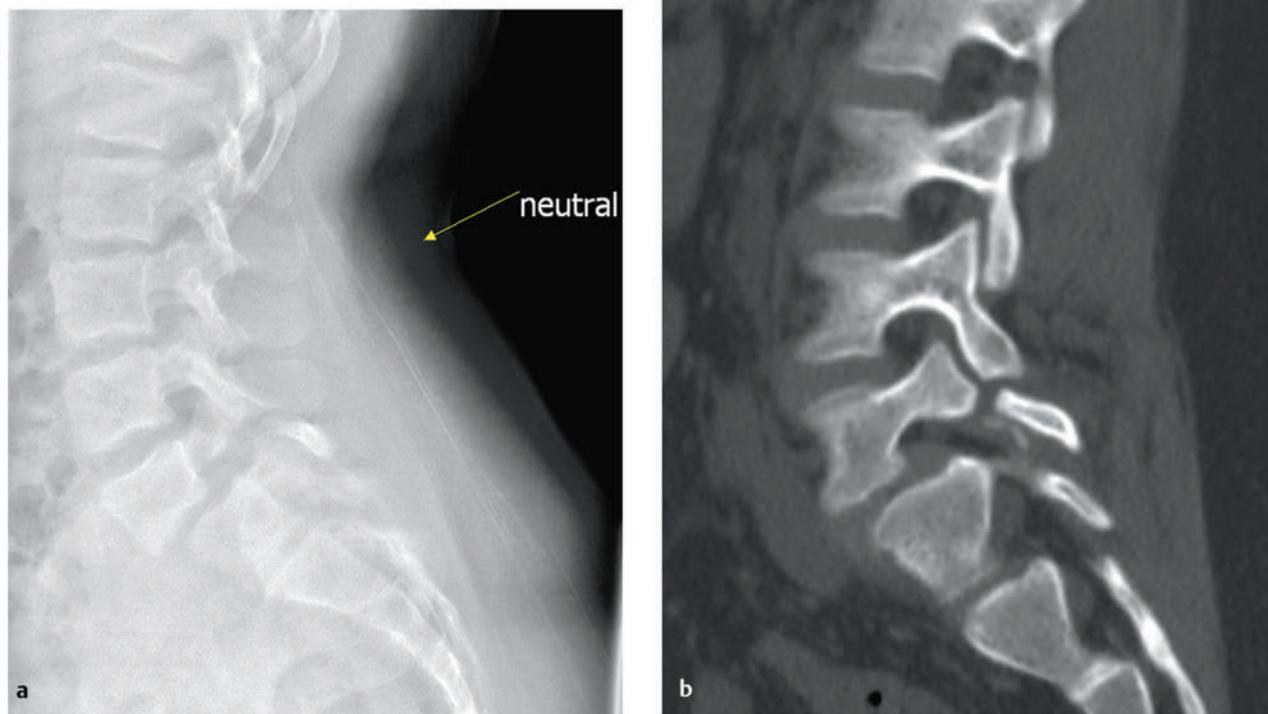


Fig. 61.18 Spondylolysis with spondylolisthesis. (a) Lateral radiograph and (b) sagittal computed tomographic scan demonstrating a chronic post-traumatic L5 pars fracture (spondylolysis) in a young girl with a Meyerding grade 2 anterolisthesis of L5 on S1.

of a lap seat belt without a shoulder harness, although they can be seen in both unrestrained and properly restrained children involved in moderate- to high-speed motor vehicle accidents.^{31,84} When a lap seat belt without a shoulder harness is used in the setting of a moderate- to high-speed decelerating force, the seat belt–abdomen interface becomes the new axis of rotation. This transfers distracting forces to the entire spinal column. The most common single level involved is L2, although flexion–distraction injuries also occur not infrequently at the thoracolumbar junction and in the lower lumbar spine.⁸⁹ Associated intra-abdominal injuries have been reported in as many as 50% of children with flexion–distraction injuries.⁹⁰

Clinical Presentation

The most common presenting symptom is back pain. Neurologic injury is rare with pure flexion–distraction because retro-pulsion of bone fragments into the spinal canal seldom occurs. Asymmetric loss of the patellar reflex may be the only presenting sign. When canal compromise is present, patients may present with paraplegia or cauda equina syndrome. Compression of neural elements is most often via retropulsed bone fragments or misalignment from kyphotic deformity. Although it occurs rarely, the application of significant traction to the spinal cord during flexion–distraction can result in cord avulsion rostral to the level of injury. Intra-abdominal or retroperitoneal injury should be suspected in any child with a flexion–distraction injury, particularly one with lower abdominal ecchymoses (“seat belt” sign). The abdominal injury often overshadows the spine injury, or vice versa, in terms of severity and the need for acute treatment. It should always be assumed that the other injury type is present until it is adequately excluded with appropriate methods.

Radiographic Diagnosis

A lateral plain radiograph is the best initial study to screen for flexion–distraction injuries. Despite this, Chance fractures can be difficult to fully appreciate on lateral plain films. CT of the thoracolumbar spine should be performed if a fracture is strongly suspected but cannot be identified on plain radiographs. The classic finding on axial CT is the “empty facet” sign wherein the inferior articular surface of the rostral vertebra is no longer in close contact with the superior articular surface of the caudal vertebra at the level of the injury. It is important not to rely on abdominal CT to rule out a Chance fracture because imaging is often obtained only in the axial plane and a horizontal fracture may be missed, even on reconstructed sagittal images.⁹¹ Separation of the facet joints and widening of the interspinous space are most commonly seen in younger children because of the increased elasticity of their ligaments. It is very rare for instability to be demonstrated on flexion–extension imaging in a child with a flexion–distraction injury and a normal static radiograph. MRI is useful to determine the amount of associated ligamentous injury and to evaluate the neural elements in rare cases of neurologic deficit. If closed or open reduction is planned, MR imaging should be performed after acute abdominal injuries are addressed to assess whether occult compressive lesions are present.

Treatment

Patients with suspected intra-abdominal or retroperitoneal injuries should undergo prompt evaluation and treatment because these injuries may be life-threatening. Flexion–distraction injuries that are not associated with neurologic deficit or significant ligamentous injury can be treated conservatively with immobilization in a thoracolumbar orthosis. Children with fluctuating or progressive neurologic deficits should undergo operative decompression, reduction, internal stabilization, and fusion. Surgical stabilization and fusion should also be considered for children who have significant associated ligamentous injuries because these are less likely to heal with conservative management alone. Glassman et al concluded from a small series of seven children that those with a kyphotic deformity of less than 20 degrees could be treated with external bracing only, whereas those with more than 20 degrees of angulation required internal stabilization and fusion because their ligamentous injuries would not be able to heal adequately, resulting in inevitable curve progression.⁹² The time elapsed since the injury is another important consideration in a decision between conservative and operative management because injuries that have gone undiagnosed for a week or longer are less likely to be reducible and heal with external immobilization. Therefore, conservative management with external immobilization in a hyperextension orthosis for 12 weeks is most appropriate in children with flexion–distraction injuries who are neurologically intact, present immediately after the injury with less than 20 degrees of kyphotic angulation, with or without bony injury, and have no neural compression. Indications for surgical decompression, reduction, and internal stabilization include more than 20 degrees of kyphotic angulation at the level of injury, late presentation, inability to achieve a closed reduction, neural compression, and fluctuating or progressive neurologic deficits (which are indicative of ongoing instability).

Fracture–Dislocation

Injury Description

Fracture–dislocation injuries are caused by compressive, tension, rotation, or shear forces that result in damage to all three columns of the thoracolumbar spine. These injuries are highly unstable, with subluxation or dislocation of the rostral vertebral levels from the caudal ones. The incidence of neurologic deficits from concomitant SCI, including complete paraplegia, is very high. Fracture–dislocation injuries may be categorized into three subtypes: flexion–rotation, shear, and flexion–distraction. The flexion–rotation subtype typically results in complete disruption of the anterior and middle columns, with anterior wedging of the vertebral body and perched or jumped facets. Of note, child abuse has been known to result in this subtype of injury.⁸³ The shear subtype occurs when the force is directed in a posterior-to-anterior direction, resulting in the disruption of all three columns, including the anterior longitudinal ligament, with anterior displacement of the rostral vertebral levels. Fracturing of both the posterior arch of the rostral vertebral level and the superior articulating facet of the caudal level is typically observed.

The flexion–distraction subtype is similar to a Chance fracture associated with lap seat belt use, except for the addition of significant anterior wedge compression (approximately 10 to 20% loss of body height) or subluxation.

Clinical Presentation

Because of the large forces and degree of spinal column translation that are often involved, the majority of patients with fracture–dislocation injuries present with neurologic deficits due to nerve root or spinal cord compression. Of those presenting with deficits, approximately half have complete paraplegia.

Radiographic Diagnosis

The hallmark of a fracture–dislocation injury is subluxation or dislocation of the vertebral column rostral to the level of injury from levels caudal to the injury. This may be demonstrated on lateral plain radiographs of the thoracolumbar spine; however, in some instances, the injury may be reduced by the time imaging is obtained. Findings that suggest a fracture–dislocation injury are an increased interspinous distance, anterior wedging of the vertebral bodies (flexion–rotation and flexion–distraction subtypes), perched or jumped facets, facet fractures, horizontal laminar fractures, and a “free-floating” lamina from complete fracture of the posterior arch of the rostral level (shear subtype). Additionally, spinous process, apophyseal, multiple rib, hip, and pelvic fractures are associated with fracture–dislocation injuries. CT through the area of interest is particularly useful in defining the injury as well as planning for operative intervention. In flexion–rotation subtypes, there is often an intact posterior vertebral body wall with rotation and offset of adjacent vertebral bodies at the level of injury, resulting in spinal canal compromise. MRI should also be obtained through the area of interest, particularly in children presenting with neurologic deficits. It is useful for assessing the degree of neural compression, evaluating for intervertebral disk disruption and herniation, and determining the amount of associated ligamentous injury.

Treatment

The definitive treatment for fracture–dislocation injuries is operative decompression and reduction of the fracture, followed by internal stabilization and fusion. The ultimate goals of surgical intervention are to prevent additional injury to the neural elements and the development of subsequent deformity. Additionally, in children with concomitant SCIs, internal stabilization allows earlier and safer participation in rehabilitation programs. This is particularly important in the pediatric population because the incidence of significant neurologic recovery following severe SCI is higher in children than in adults.⁹³ A better prognosis is associated with younger age and an incomplete neurologic injury.

Apophyseal Ring Fracture

Injury Description

Apophyseal ring fractures are uniquely pediatric injuries in which a flexion mechanism results in fracture of the posterior

rim of the immature vertebral body end plate (the ring apophysis).⁸³ They most typically involve the adolescent lumbar spine. Retropulsion of the osseous fragment into the spinal canal, which can mimic a herniated intervertebral disk, may occur.

Clinical Presentation

The clinical presentation is similar to that of a herniated intervertebral disk. Symptoms typically include back pain with or without radicular findings, including radicular pain or weakness.

Radiographic Diagnosis

Apophyseal ring fractures may be difficult to appreciate on plain radiographs. CT or MR imaging may be needed to obtain a diagnosis. Given that a large number of patients present with symptoms similar to those seen with a herniated intervertebral disk, MRI is probably the best initial adjunct to plain radiographs. Additional unnecessary radiation exposure is also avoided in this case. Imaging will typically demonstrate fracture of the posterior aspect of the vertebral body end plate.⁹⁴ Retropulsion of an osseous fragment into the spinal canal may be seen on CT or MR imaging.

Treatment

Conservative management, including pain control, anti-inflammatory medications, physical therapy, and bracing, is typically the initial treatment for apophyseal injuries. Patients with large, centrally retropulsed bone fragments are at a higher risk for the development of chronic back pain.⁹⁵ Operative intervention is generally reserved for patients with retropulsed bone fragments and neurologic symptoms, or for those with pain refractory to conservative management.⁸³ Surgical management includes decompression with internal stabilization and fusion. Although historically anterior surgical approaches have been used to treat apophyseal avulsion fractures that occur at levels above the conus medullaris, posterolateral approaches for anterior decompression, posterior instrumentation, and anterior–posterior fusion have become more popular in recent years.

Spondylolysis and Spondylolisthesis

Injury Description

Spondylolysis is a defect of the pars interarticularis that may develop from repeated microtrauma (► Fig. 61.18, ► Fig. 61.19). It is found most commonly in adolescents who engage in physical activity, such as gymnastics and football, that involve repeated hyperextension.³⁰ The most commonly affected level is L5–S1, followed by L4–5. Spondylolysis can result in anterior spondylolisthesis of the cephalic, relative to the caudal, vertebral body. The Meyerding classification is the most widely accepted classification system for spondylolisthesis, with grades 1 and 2 being low-grade slips (<50% displacement) and grades 3 through 5 (>50% displacement) being high-grade slips.⁹⁶ Factors that are associated with the progression of spondylolisthesis are a diagnosis before the adolescent growth spurt, high-grade spondylolisthesis, and female gender.³⁰

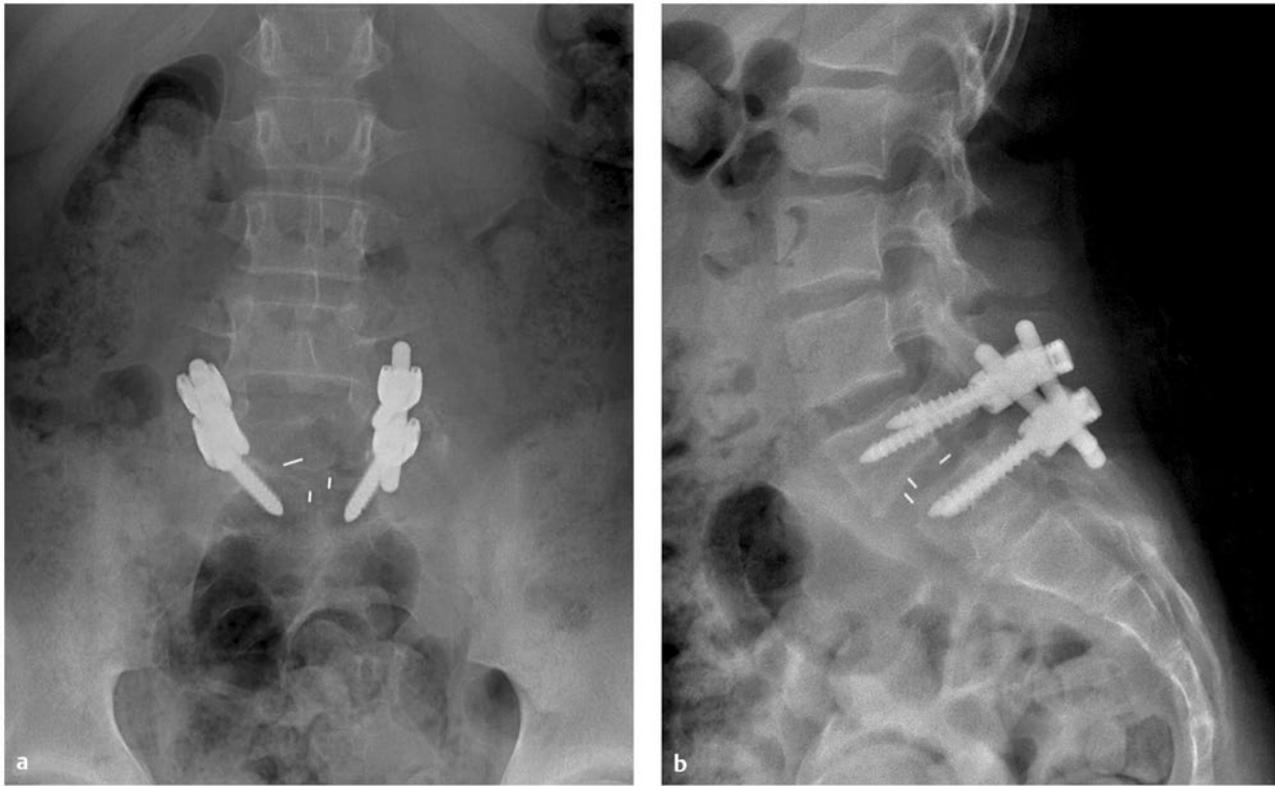


Fig. 61.19 Spondylolysis with spondylolisthesis. Postoperative (a) anteroposterior and (b) lateral radiographs demonstrating L5–S1 transforaminal interbody fusion and L5–S1 posterior segmental instrumentation performed in the same patient as in ▶ Fig. 61.18.

Clinical Presentation

Patients most commonly present with back pain exacerbated by activity. Radicular symptoms and neurologic deficit may also be present, particularly with higher-grade slips. A step-off may be detected on palpation of the spine in high-grade spondylolisthesis. Hamstring tightness is another frequent physical examination finding.³⁰

Radiographic Diagnosis

Spondylolysis and spondylolisthesis may both be demonstrated on lateral plain radiographs of the lumbar spine (▶ Fig. 61.18a). Grading of the degree of spondylolisthesis is also readily obtained from plain films. CT should be considered if spondylolysis is suspected but a pars defect is not clearly identified on X-ray and when operative intervention is planned (▶ Fig. 61.18b). MR imaging should be obtained when there is a neurologic deficit to appropriately evaluate the neural elements. It should also be considered in instances of high-grade spondylolisthesis to evaluate for associated intervertebral disk compromise or herniation because these may influence subsequent management.

Treatment

Acute spondylolysis with or without low-grade spondylolisthesis can be managed conservatively with activity modification,

pain medications, and bracing. Operative intervention for spondylolysis is rarely needed but is indicated if symptoms are refractory to conservative treatment; it is also indicated for progressive slips and spondylolysis with high-grade spondylolisthesis.³⁰ For isolated spondylolysis without spondylolisthesis, surgical intervention is typically geared toward a direct pars repair. If low-grade spondylolisthesis is present, in situ instrumentation with posterolateral fusion is the most common approach. Alternatively, high-grade spondylolisthesis is generally treated via partial reduction and decompression with instrumented fusion. This is most commonly accomplished through a posterior approach, such as a posterior or transforaminal lumbar interbody fusion (PLIF, TLIF), although an anterior approach with anterior grafting (i.e., anterior lumbar interbody fusion, ALIF) may be considered (▶ Fig. 61.19a,b).

SCIWORA

Injury Description

A detailed discussion of the medical management and outcomes of spinal cord injury without radiographic abnormality (SCIWORA) is beyond the scope of this chapter. However, the pathophysiologic basis for its occurrence are the specific anatomical and biomechanical properties of the pediatric spinal column discussed in Chapter 60. First described by Pang and

Wilberger in 1982, before the routine use of MRI, the term SCIWORA has historically been applied to traumatic myelopathy without fracture or subluxation identifiable on plain films or CT.⁹⁷ Two decades later, Pang published a review of SCIWORA summarizing the wealth of new information reported on the topic after its initial description.⁹⁸ SCIWORA is a uniquely pediatric injury resulting from the inherently increased flexibility of the developing spinal column. It primarily affects younger children and is associated with a high incidence of neurologic injury. SCIWORA results because the developing spinal column is more elastic than the mature spine and therefore able to accommodate significant intersegmental displacement at the moment of injury without fracture or ligamentous rupture. Horizontally oriented facets,^{71,99,100} wedge-shaped vertebral bodies,^{72,99} and an absence of uncinatous processes in the cervical spine³⁶ additionally contribute to the susceptibility of the pediatric spinal column to intersegmental movement. Hyperextension, flexion, distraction, and ischemic mechanisms have been implicated in SCIWORA. The displacement is momentarily large enough to cause significant SCI and is followed by spontaneous reduction of the dislocated segments. The result is a normal radiographic appearance of the spinal column on plain radiographs and CT.¹⁰¹

Age is associated with SCIWORA in three important ways. First, in children with traumatic myelopathy, the incidence of SCIWORA is higher in younger (0 to 9 years) children. Conversely, severe SCI in older children is more commonly associated with frank vertebral column disruption.³¹ Second, younger children with SCIWORA generally have more severe SCI than older children do.¹⁰² Third, SCIWORA most commonly affects the upper cervical spine in young children, whereas in older children the incidence of injury to the lower cervical levels is increased. This is explained by the high degree of inherent flexibility in the cervical versus the thoracic spine and the fact that the fulcrum for maximal flexion-extension is at a progressively lower level within the subaxial cervical spine as the spinal column matures (C2-3 in infants, C3-4 by the age of 5 to 6 years, and C5-6 in adolescents and adults). Conversely, SCIWORA involving the thoracic cord is distributed evenly in all pediatric age groups because the thoracic spinal column matures more gradually than the upper cervical spine.¹⁰² SCIWORA involves the thoracic cord in approximately 15% of cases and generally occurs after violent trauma with severe distraction (i.e., high-speed motor vehicle accidents or lap seat belt use) or posterior-to-anterior crush injuries (i.e., children crushed by a slow-moving vehicle and presenting with tire tracks on the back).¹⁰²⁻¹⁰⁹

In addition to the initial SCI, SCIWORA results in occult instability of the spinal column. Although the stabilizing ligaments and soft tissues of the spine are elastic enough to undergo transient stretching and recoil without rupture, MRI findings indicate that they are often partially torn or severely sprained.^{36,110} In this situation, the spinal column is vulnerable to excessive motion with repeated, even innocuous, stress. This places the spinal cord at further risk, and it may be reinjured if the occult instability is not properly treated, resulting in delayed neurologic deterioration and recurrent SCIWORA.

Clinical Presentation

Children with SCIWORA generally present with traumatic myelopathy, most frequently localized to the cervical spine. Some children with SCIWORA (22 to 67%) do not have immediately detectable neurologic deficits; rather, the deficits develop in a delayed fashion after a period of minutes to days.^{81,97,106,110-113} This phenomenon may be explained by undiagnosed occult instability of the spinal column resulting from the initial trauma, predisposing the affected child to repeated spinal cord insults and subsequent neurologic injury from only minor forces. This concept is supported by observations that SCIWORA may recur up to 10 weeks after the initial trauma.¹¹⁴ Importantly, neurologic deficits from recurrent SCIWORA are generally more severe than those from the initial injury.¹¹⁴ Children with thoracic SCIWORA have a high incidence of associated thoracic, abdominal, and pelvic injuries.

Radiographic Diagnosis

The radiographic evaluation of a child with a neurologic deficit begins with a complete spine survey. If plain films are normal, fine-cut CT through the level of the deficit is obtained to assess for occult fractures. SCIWORA, by definition, does not result in abnormalities of the spinal column, such as fractures or evidence of gross instability (i.e., subluxation), on static or dynamic plain films or on CT. Rather, SCIWORA results in occult instability, in contrast to the overt instability seen in spinal column injuries like fracture-subluxation and subluxation without fracture (purely ligamentous injuries).^{36,71,99,100,110,115} Associated muscle spasm following spine trauma has been demonstrated to obscure even gross instability; therefore, the concept of occult instability is not contradicted by the failure of dynamic imaging to demonstrate pathologic movement.¹¹⁶

Prompt MR imaging is crucial in the evaluation of children with neurologic deficits localizing to the spinal cord. In children with SCIWORA, MRI frequently demonstrates abnormalities of the neural and extraneural soft tissues of the spine.¹¹⁷ Extraneural findings correlate with the mechanism of injury and correspond to the level of the neurologic deficit.³⁶ Typical findings include partial tearing or rupture of the anterior longitudinal ligament (hyperextension) or posterior longitudinal ligament (hyperflexion), intravertebral disk hemorrhage (translational/shearing forces), tectorial membrane tearing and hemorrhage, and interspinous and interlaminar ligament hemorrhage (distraction). Because extravasated blood is converted within hours to methemoglobin in nonneural tissues, extraneural injuries associated with SCIWORA are discernable on T1-weighted MR imaging sequences very soon following injury.³⁶ The majority of patients with SCIWORA will also have neural tissue injury demonstrable on MRI, including complete disruption of the spinal cord, major cord hemorrhage (>50% of the cross-sectional area of cord), minor cord hemorrhage (<50% of the cross-sectional area), or spinal cord edema only.³⁶ Although approximately one-quarter of patients with SCIWORA will fail to demonstrate any spinal cord abnormality on MR imaging, the vast majority

of them will have demonstrable ligamentous injury. Therefore, in the modern era, SCIWORA should be used to describe patients with neurologic injury who have no radiographic abnormalities on any imaging study, including plain and dynamic radiographs, CT scans, and MR images.

Treatment

Like that of any case of suspected spine or spinal column trauma, the management of a child with SCIWORA begins in the field with prompt immobilization and resuscitation. As discussed in Chapter 60, care must be taken in infants and young children to prop up the thorax from the shoulders down to maintain a neutral alignment and avoid inadvertent flexion of the neck. SCIWORA should be considered a diagnosis of exclusion. In a child with a neurologic deficit, it is imperative to rule out head trauma, compressive lesions of the spinal cord (i.e., epidural hematoma, intervertebral disk herniation), and injuries resulting in gross instability (i.e., fractures, purely ligamentous injury) as causes of the deficit because these may require more specific and prompt surgical intervention. This is achieved through a combination of static and dynamic plain radiographs, fine-cut CT, and MR imaging, as previously discussed. Patients with cervical or thoracic SCIWORA should be initially maintained with a hard collar or with strict bed rest and log rolling only, respectively. Based on the results of the National Acute Spinal Cord Injury Study II (NASCIS II), children with nonpenetrating SCIs, including SCIWORA, whose injury is diagnosed within 8 hours of onset are generally begun on a 24-hour course of high-dose corticosteroids.¹¹⁸

SCIWORA results in occult instability of the spinal column wherein the spinal cord is vulnerable to repeated injury during seemingly normal activity or minor trauma. This may result in delayed neurologic deficits that are more profound than those of the initial SCI. The primary treatment for children with SCIWORA is external immobilization with a rigid cervical brace (for cervical SCIWORA) or a thoracolumbar orthosis (for thoracic SCIWORA) and activity restrictions for several months. Some authors have reported repeated injury after only 2 months of immobilization, but no recurrent injuries when the duration of immobilization was at least 3 months.³⁶ Repeated flexion–extension radiographs should be obtained in a delayed fashion to assess for late instability.

61.2 Conclusion

There exists a wide array of possible injury types following trauma to the pediatric spinal column. A thorough understanding of the underlying anatomical, biomechanical, and neurologic consequences of these injuries, along with their associated clinical and radiographic findings, is necessary for their prompt and appropriate management through both nonoperative and surgical techniques.

Pearls

- AOD should be suspected in any child involved in an appropriate high-velocity mechanism (i.e., a pedestrian–motor vehicle accident), especially one presenting with facial injuries or initial cardiopulmonary instability.
- AOD may result in subtle radiographic findings. Because early diagnosis is paramount to mitigate additional, potentially catastrophic neurologic injury, when AOD is suspected there should be a relentless pursuit of findings to either confirm or exclude the diagnosis.
- True odontoid fractures are rare in children. Rather, they are frequently epiphysiolysis at the dentocentral synchondrosis, located just below the base of the dens in the rostral C2 body, which is not fused until 8 to 11 years of age.
- Traumatic injuries to the subaxial cervical spine are most efficiently classified into purely ligamentous injuries, osseous anterior column injuries, osseous posterior column injuries, and combined anterior and posterior column injuries.
- Thoracic and lumbar spinal column injuries are much less frequent than cervical injuries in the pediatric population. Similar injury types are seen in both the thoracic and lumbar spine; of these, fracture–dislocations are most commonly associated with neurologic deficits.
- Apophyseal ring fractures may mimic a herniated intervertebral disk; however, typically they are less likely to respond to conservative management and more frequently require surgical intervention.
- SCIWORA results in occult instability of the spinal column, with a significant risk for repeated injury to the spinal cord and profound delayed neurologic deficits after even minor or innocuous trauma. Prompt treatment with external immobilization is warranted.

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62 Spinal Cord Injury

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Trauma is the leading cause of death and disability in the pediatric population. Spinal cord injuries, despite involving only 1 to 2% of all pediatric trauma cases, can be incredibly debilitating, requiring a lifetime of care and utilization of medical resources.¹⁻⁷ Spinal cord injury (SCI) affects approximately 2 per 100,000 children per year, and the National Spinal Cord Injury Statistical Center (NSCISC) found in 2010 that 9.86% of patients with SCI were younger than 18 years.^{8,9} The vast majority of injuries involve the cervical spinal cord, whereas only 5.4 to 34% involve the thoracolumbar spine.^{1,8,10,11}

The pediatric spine is not merely a miniature version of the adult spine. Instead, the developing spinal column is inherently more elastic and mobile. The hypermobility of the pediatric spine provides less protection to the fragile, underlying spinal cord.¹² A newborn spine and a 14-year-old spine lie along a biomechanical continuum that becomes less mobile and more rigid as a child transitions into late adolescence and adulthood. The differences between adults and children are not limited to biomechanics; rather, there are clinically important differences in regard to injury pattern, treatment, rehabilitation, and outcomes.

62.1 Epidemiology

The epidemiology of pediatric SCI is difficult to characterize fully because of the limited available data on this patient population.¹³⁻¹⁵ The extant literature contains few studies that include pediatric patients, typically excluding those treated at adult institutions, who die before arrival at a hospital, or who have birth-related SCI. Potential evidence as to the degree of underreporting in children can be extrapolated from adult data. Most authorities illustrate the increased susceptibility of the pediatric spine to injury. Milby et al, in a pooled analysis of 281,864 adult patients with trauma, found a prevalence of SCI of 3.7% in the adult population.¹⁶ One would expect that pediatric patients with trauma would have an incidence of SCI above 1%.

The incidence of SCI is approximately 1.99 to 7.4 per 100,000, and approximately 1,455 children are admitted each year in the United States with SCI.^{8,17-19} The prevalence within the pediatric population is poorly characterized but can be estimated based on age at injury. The prevalence of SCI in both adults and children is between 223 and 1,009 per million inhabitants, with fewer than 10% of injuries occurring before the age of 18 years.^{13,14} Lasfargues et al demonstrated the prevalence of SCI in the United States in 1988 to be 176,697, with 11,745 (6.6%) of patients younger than 24 years.²⁰ The NSCISC found in 2010 that 9.86% of patients with SCI were younger than 18 years.⁹ The same data demonstrated that only 1% of spinal cord injuries occurred in patients younger than 13 years. There is an obvious age distribution, with a mean age of 10.3 to 13.5 years and a median age closer to 16 years.^{6,21} Younger patients have a lower rate of SCI, and the incidence rapidly increases with age. Although motor vehicle accidents remain the leading cause of SCI across all age groups, the age of the victim is also pertinent

to the mechanism of injury. Older persons tend to engage in higher-risk activities, whereas younger people are more susceptible to nonaccidental trauma. The gender distribution tends to be more even in younger patients, with the male-to-female ratio of persons with injuries increasing toward adolescence and adulthood.⁴

Pediatric SCI is more common in males, with reported male-to-female ratios as high as 3:1.^{4,8,21-24} The gender distribution is a result of increased risk-taking behavior as children age. Sports-related injuries are rarely seen before the age of 9 years. After 9 years of age, sports-related injuries contribute to approximately 25% of pediatric cases of SCI in the United States, and most of these occur in males.²¹ Brown et al demonstrated that the numbers of males and females involved in motor vehicle collisions were almost equal, with a male-to-female ratio of 1.2:1, but for sports-related injuries, the ratio was 3.5:1.²¹

Race also appears to play a role in the epidemiology of pediatric SCI. In the United States, Caucasians have the highest rate and account for the majority of cases of SCI. African Americans exhibit the second highest rate of SCI (1.53 per 100,000), followed by Native Americans (1.00 per 100,000), Hispanics (0.87 per 100,000), and Asians (0.36 per 100,000).^{8,19}

Pediatric SCI is a rare disease entity and as such is not a major international public health concern. Consequently, few geographic data exist outside the developed world. Several interesting cultural trends are apparent from the available literature. Cripps et al performed a global epidemiologic review of SCI and made several observations. In Turkey, a high percentage of SCIs occur after falls from rooftops because children often sleep on the roof in summer.¹³ Southern Asia, specifically Nepal and Pakistan, have a similarly high incidence of falls from rooftops and trees that result in SCI.^{13,25} In Greece and Italy, young males are known for engaging in high-risk driving behaviors that place them at increased risk for SCI.^{7,26} Epidemiologic studies in the pediatric population would be most helpful in terms of directing future research into prevention and management of patients with SCI.

62.2 Biomechanics and Anatomy

The biomechanics of the developing spine and spinal cord have been the subject of much discussion but little research because of the difficulty in conducting the studies in children. Nonetheless, the developmental anatomy and subsequent biomechanical differences in the pediatric spine are felt to play a central role in the understanding of pediatric spine trauma.

Embryology is always a fitting starting point for understanding any anatomical process. The developing fetal spine derives from paraxial mesoderm that is located lateral to the neural tube. The paraxial mesoderm develops into paired somites that then form the axial skeleton and its associated ligaments, tendons, and muscles.^{27,28} The demarcation of individual vertebrae takes place through a process known as resegmentation, in which the anterior and posterior portions of adjacent somites fuse.^{27,29,30} Each vertebral body is thus formed from

two sclerotomes, unlike the peripheral nervous system. The intervertebral disks are formed at the boundary between the anterior and posterior sclerotomal portions of the somite.²⁸ The development of the spine begins in utero and continues until early adulthood.

Ossification of the atlas and axis is unique compared with that in the remainder of the subaxial spine. The anterior arch of C1 is typically ossified by the age of 1 year, and complete ossification of the posterior arch occurs around the age of 3 years.³¹ The atlas achieves a normal adult radiographic appearance by the age of 7 years.³² The axis is more complex in that there are a total of six ossification centers (unlike the typical four at other spinal levels); these are involved in the formation of the odontoid process. The odontoid process begins to fuse to the body of C2 between the ages of 3 and 6 years.³² This process is normally completed by the age of 11 years.³² Ossiculum terminale is a condition in which the secondary ossification center at the apical portion of the odontoid does not fuse by the age of 12 years.³³ Ossiculum terminale is commonly seen on adult radiographs and usually carries no clinical significance, although several case reports suggest there may be an association with atlantoaxial instability.³⁴ Mortazavi et al noted that the C2 posterior arch fuses in the midline by the age of 3 years and with body between the ages of 3 and 6 years.³³

Os odontoideum, a nonunion of the synchondrosis of the odontoid process that is associated with pathologic instability, is clinically distinct from ossiculum terminale. Radiographically, the two can be differentiated by the location of nonunion. Os odontoideum is considered by most authorities to be inherently unstable regardless of findings on dynamic plain films. Klimo et al described three patients with known os odontoideum who were followed nonoperatively and experienced SCI.³⁵ Surgical management is thus recommended to minimize risk for subsequent SCI (see box “Predisposing Conditions for Spinal Cord Injury (p.834)”).

Predisposing Conditions for Spinal Cord Injury

- Congenital cervical stenosis
- Down syndrome
- Morquio syndrome
- Chiari type 1 malformation
- Os odontoideum

The subaxial cervical spine from C3 to C7 typically follows a very similar ossification pattern. The ossification of the posterior arch follows the same pattern as C2, and the posterior arch is typically fused with the body by age 6. Complete ossification typically does not occur until age 25.³² Central to an understanding of spinal radiographs in children is the ability to recognize epiphyseal variants, incomplete ossification of synchondroses and apophyses, unique vertebral architecture, pseudosubluxation of C2 on C3, overriding of the anterior atlas in relation to the odontoid in extension, and varied atlantodental intervals.^{36–40} The pediatric spine is thus unique in terms of stability, injury patterns, clinical and radiographic evaluation, and treatment (► Fig. 62.1a–c).

The stability of the spine is a function of the connecting ligaments, facets and articular capsules, intervertebral disks, and associated musculature. The increased proportional weight of a child's head with respect the remainder of the body increases the mechanical strain on the cervical spine during extremes of flexion, extension, rotation, and distraction.^{12,41,42} The neck acts as a fulcrum, and the larger head effectively lengthens the moment arm, thus increasing the force placed upon the underdeveloped cervical spine. In addition to the increased forces acting on the spine, the pediatric cervical diskoligamentous complex has been shown to be considerably more elastic than that in adults.^{32,38,42–45} The ramifications of increased elasticity are that the spine can bend but not break during trauma. Unfortunately, the spinal cord does not well tolerate stretching and is thus felt to be more susceptible in the pediatric population. The ligaments, joint capsules, and intervertebral disks have different characteristics, as does the bony anatomy of the articulations themselves.

The occipitoatlantoaxial joints are an incredibly complex bony and ligamentous region of the most cephalic portion of the spinal column and are involved in many pediatric SCIs. The occipital condyles, although infrequently fractured, have associated ligamentous structures involved in atlanto-occipital dislocation.^{46,47} Additionally, the shape of the occipital condyle and the shallow articulation with the lateral mass of C1 put the vertebral artery at risk for injury during hyperextension.⁴⁸

Pang and Zovickian have written several overviews of the morphometric differences between the adult and pediatric cervical spine that have implications with regard to spinal cord injuries.^{12,42} They explain that the facet joints are “... shallow and oriented more horizontally than in adults,” and this is felt to increase the potential for unintended translation.^{12,42} The potential for forward translation is also increased in children by the anterior wedging of vertebral bodies.^{32,42–44} The uncovertebral joints (joints of Luschka) are stabilizing joints of the subaxial spine that chiefly limit lateral movement.⁴⁹ Orofino et al studied the uncovertebral joints of 11-week-old fetuses to full-term infants and found no synovial tissue at the future site of the uncinat process, confirming observations in adults that the uncovertebral joints are not true synovial joints.⁵⁰ Despite not being true synovial joints, unlike the facets, they do provide a mechanical advantage in preventing lateral movement and a degree of rotation.^{33,51} The uncinat processes and uncovertebral joints are not formed until around the age of 10 years and continue to develop into adulthood.^{49,52} The incompletely developed subaxial spine contributes to instability and increases the risk for SCI in children.

The diameter of the spinal canal is another important consideration. According to Steel's “rule of thirds,” which was proposed in 1968, the spinal canal at C1 is filled with (1) odontoid process, (2) spinal cord, and (3) cerebrospinal fluid “dead space” in equal proportions.^{53–55} Jauregui et al found that Steel's rule of thirds is maintained throughout childhood, with the average diameter available for the spinal cord in neonates being approximately 12.4 mm.⁵³ The median diameter of the canal at C2 was found by Wang et al to increase from between 12.27 and 12.79 mm at 6 months to between 15.75 and 16.00 mm at 13 years.³¹ After 13 years of age, the diameter of the spinal canal stabilizes to the adult range. When the smaller canal diameter is coupled with forces that result in hyperextension, the spinal

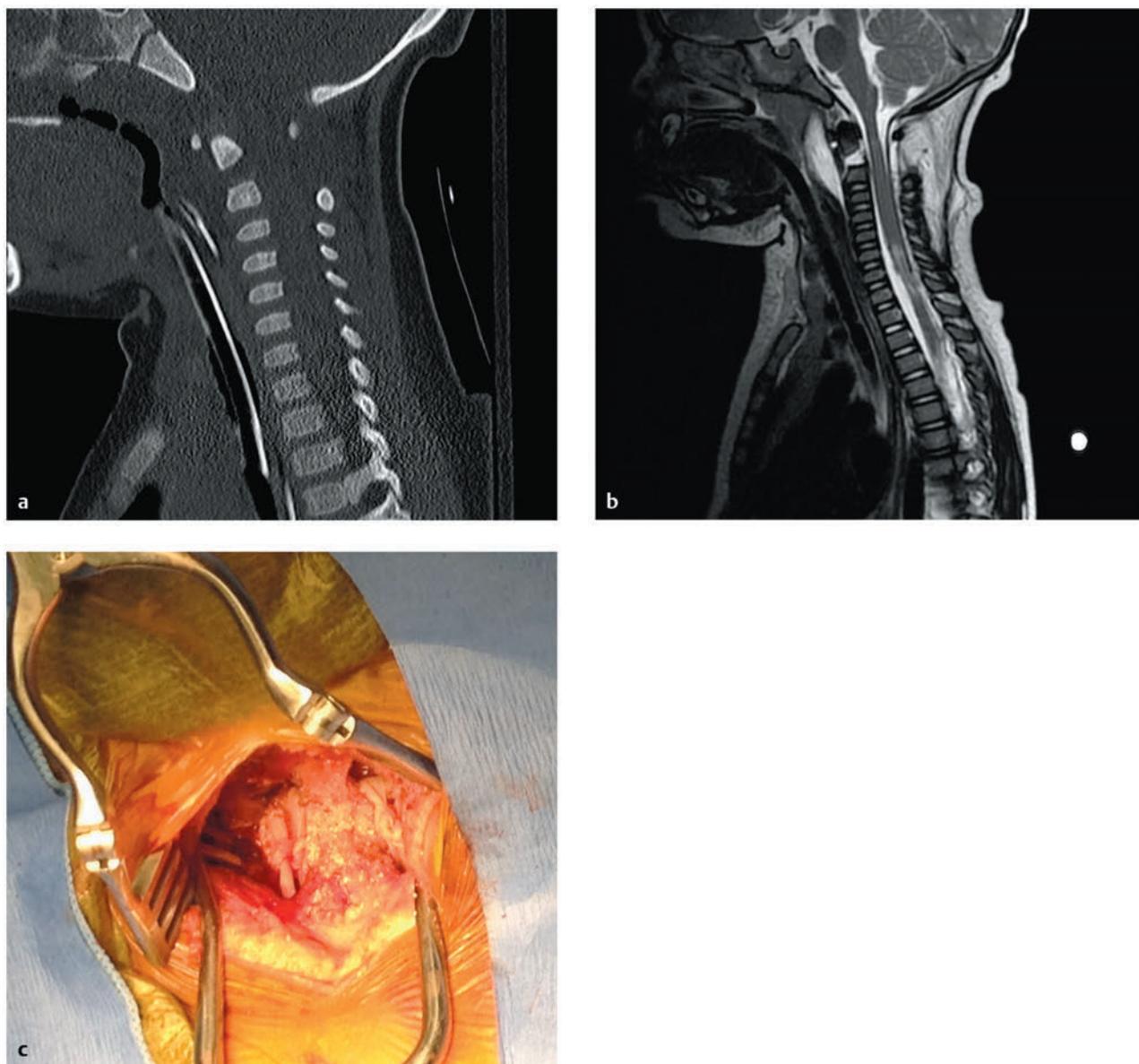


Fig. 62.1 An 18-month-old girl in a forward-facing car seat during a motor vehicle collision. (a,b) The patient presented with an American Spinal Injury Association (ASIA) class A spondylolisthesis fracture of C2 that was placed in a halo. (c) The patient subsequently underwent internal fixation with Mersilene (Ethicon, Somerville, NJ) tape between C1 and C2.

canal diameter can be further decreased by up to 50% simply from the inward buckling of the ligamentum flavum.^{12,56–58}

62.3 Thoracolumbar Injuries

Thoracolumbar fractures most often occur in older children and infrequently lead to SCI (14.6%).¹¹ Dogan et al reviewed 89 patients with thoracolumbar injuries and found motor vehicle accidents to be the most common mechanism.¹¹ The classification

of thoracolumbar fractures in the pediatric population is not characterized, but the thoracolumbar injury classification and severity score (TLICS) may be used.^{59,60} For instance, purely ligamentous injuries (1.1%) without any bony involvement are classified as distracting injuries with interruption of the posterior ligamentous complex. The utility of the TLICS system in children is the consideration of ligamentous involvement and the neurologic examination (see box “Thoracolumbar Injury Classification and Severity Score” and ► Fig. 62.2a,b).

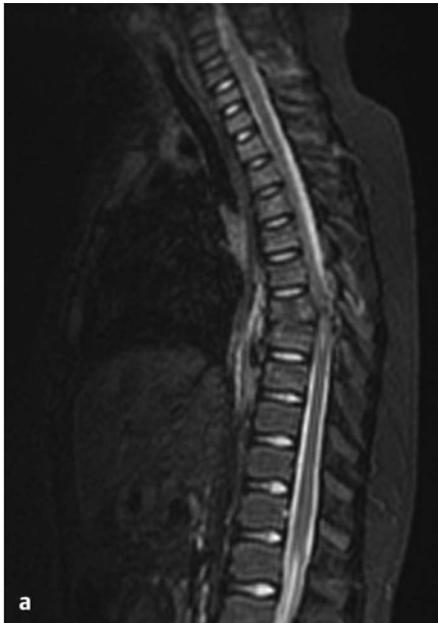


Fig. 62.2 An 11-year-old girl unrestrained in a motor vehicle collision presented with an American Spinal Injury Association (ASIA) class A injury at the T7 level. (a) Her thoracolumbar injury classification and severity score (TLICS) was as follows: morphology, 3; posterior ligamentous injury, 3; neurologic injury, 2. (b) The patient underwent decompression, internal fixation, and fusion. She now ambulates with a walker (ASIA class D) and has normal bowel and bladder function.

Thoracolumbar Injury Classification and Severity Score

Injury morphology

- Compression
- Burst
- Translational/rotational
- Distraction

Integrity of posterior ligamentous complex

- Intact
- Suspected/indeterminate
- Injured

Neurologic status

- Intact
- Nerve root
- Complete: American Spinal Injury Association (ASIA) class A
- Incomplete
- Cauda equina syndrome

62.4 Birth Injuries

Birth-related SCI is rare and is estimated to affect approximately 1 in 60,000 live births.^{61–63} Birth injuries are difficult to diagnose and are a highly litigated form of pediatric SCIs.^{63–65} The neurologic examination in a neonate is difficult. Normal reflexes can mask an underlying complete cord transection. Upper cervical SCI can present with respiratory insufficiency, hypotonia, and quadriplegia. Lower cervical SCI demonstrates abdominal breathing (due to paralyzed intercostal muscles) in addition to lower extremity hypotonia.⁶³ An important and underappreciated element in the examination of a neonate is the facial reaction to painful stimuli. Reflexive withdrawal of the extremities without grimacing or crying is the hallmark of neonatal SCI. Additionally, Horner syndrome or brachial

plexus injury provides evidence of a difficult delivery and potential SCI.

Not all cases of neonatal SCI occur during delivery; multiple reports in the literature document prenatal SCI.^{63,65–67} The management of birth-related SCI requires ascertaining a diagnosis and evaluating for potential operative intervention. Blount et al described a spontaneous cervical epidural hematoma that mimicked a birth-related SCI and later required surgical decompression.⁶⁵

62.5 SCIWORA

SCI without radiographic abnormality (SCIWORA) is a subtype of SCI that was initially described by Pang and Wilberger in 1982.⁶⁸ They described 24 patients with SCI on examination without imaging abnormalities on plain films, computed tomography (CT), or myelography. Magnetic resonance (MR) imaging, a nonradiographic form of imaging, is abnormal in approximately 15 to 65% of patients with SCIWORA.^{62,69} Thus, the presence of neural or extraneural abnormalities on MR imaging does not exclude the diagnosis, although the semantics of the term remain controversial. For instance, a patient with instability on flexion–extension radiographs does not have SCIWORA, but ligamentous hyperintensity on STIR (short tau inversion recovery) MR imaging suggesting instability would not preclude the diagnosis. Further standardization of the term will limit confusion in the literature and clinical setting. The incidence of SCIWORA in the pediatric population with SCI is 34.8% (range, 5 to 67%).⁷⁰ As mentioned previously, the spinal column elasticity of younger children leads to a higher rate of SCIWORA.⁷¹

The 2012 Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries, citing level 3 evidence, recommend that the initial evaluation of a patient with SCIWORA include MR imaging, radiographs of the entire spinal column, and flexion–extension plain films.⁶⁹ Normal MR imaging portends a good outcome. Bosch et al and Pang independently reported complete recovery in all patients with SCIWORA who

had normal MR imaging ($n = 50$).^{70,72} There are small case studies of patients with normal MR imaging and deficits persisting beyond 1 year.⁷³ Pang further stratified findings into major hemorrhage, minor hemorrhage, and edema.⁷⁰ The degree of SCI seen on MR imaging was directly related to outcome.

MR imaging findings can vary depending on patient age and on the level, mechanism, and extent of injury. MR imaging in the acute setting may identify cord signal change, compressive lesions, and/or ligamentous injury. Epidural hematomas, disk herniations, and other compressive lesions resulting in SCIWORA require operative decompression. MR imaging also can demonstrate ligamentous injuries, especially on T2 and STIR sequences, that suggest instability.^{72,74,75} Mortavazi et al restated the previous recommendations of Pollack et al from 1988 to repeat MR imaging 6 to 9 days after the initial injury.^{33,76} The quality of MR imaging and the sequences performed have changed significantly since 1988. Nonetheless, in a patient with normal initial MR imaging and a persistent neurologic deficit, repeated imaging is warranted (► Fig. 62.3a–c). Flexion–

extension lateral radiographs are potential adjuncts to clearing the cervical spine and ruling out instability in SCIWORA. Paraspinal muscle spasms may prevent adequate flexion for several days after injury.⁷⁷ Pang also recommends somatosensory evoked potential (SSEP) testing in all patients with SCIWORA, although the clinical utility is not well characterized in the literature.

The surgical treatment of patients with SCIWORA depends on the presence of compressive pathology and/or instability. The vast majority of patients, however, will not have a surgical indication. Activity restriction thus becomes important to promote recovery and prevent recurrent injury. Pollack et al studied 8 patients (19%) with recurrent SCIWORA and found most surgical indications to occur within the first week (62.5%) and all to occur within 10 weeks.⁷⁶ As a result of this and similar studies, external immobilization is recommended for up to 12 weeks following injury, and patients are encouraged to avoid “high-risk” activities for 6 months.^{12,69,76}

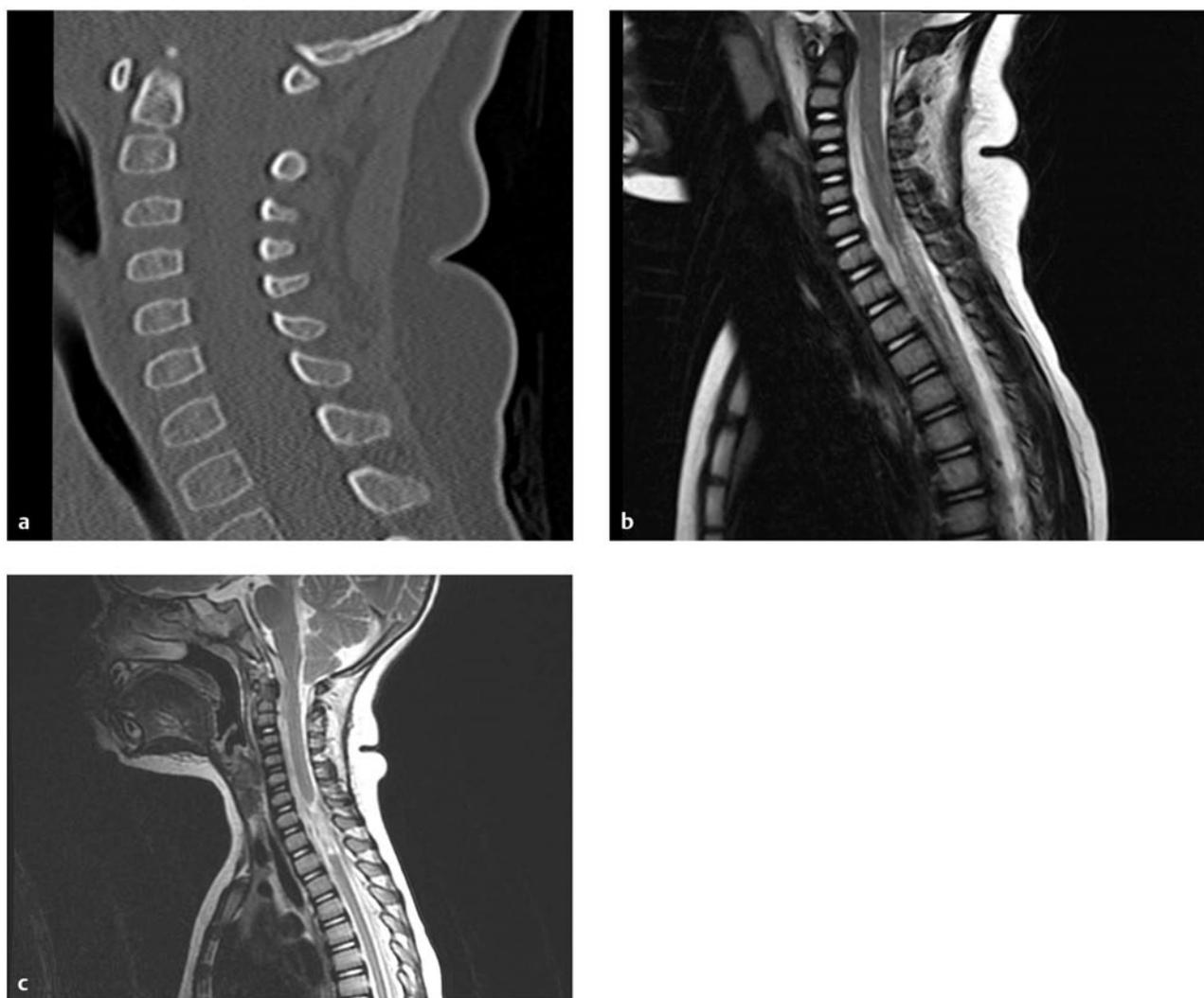


Fig. 62.3 A 2-year-old boy after a motor vehicle collision with a T2 level American Spinal Injury Association (ASIA) class A injury and no discernible spinal column injury. (a) Image obtained less than 24 hours after injury. (b) Image obtained 9 days later demonstrates retraction of the severed cord ends. (c) Two years after injury, late instability had not developed.

62.6 Initial Stabilization and Evaluation

The management of pediatric cervical spine injuries begins immediately at the scene of the accident. Education of the general public and emergency medical personnel is a vital adjunct to in-patient care. The first step in the initial evaluation of any trauma is management of the airway, breathing, and circulation. Maintaining adequate oxygenated perfusion to the injured spinal cord is a central tenet in management and should begin as quickly as possible.⁷⁸ During the primary survey, the cervical spine should be held in in-line immobilization and manipulated as little as possible. A cervical collar of appropriate size should be placed, or the head should be immobilized with rolls. A collar that is too large will not provide adequate immobilization and may place the cervical spine in excessive distraction. Because the head-to-body ratio is larger in children than in adults, patients less than 8 years old should be placed on a back board with either an occipital recess or thoracic bolsters to avoid untoward cervical flexion and maintain neutral alignment.^{79,80} The proper initial treatment of a child with an unstable cervical spine may prevent secondary SCI.

Following the initial evaluation and stabilization, a more in-depth assessment of the patient must be performed. The clinical history and physical examination are paramount to medical decision making regarding radiographic evaluation and the potential treatment of any injuries. There is no level 1 evidence in pediatric spine trauma, but level 2 and 3 evidence provides some guidance on imaging.

In the absence of a neurologic deficit, patients who are awake, alert, communicative, without midline cervical tenderness, not intoxicated, and without painful distracting injuries typically do not need cervical spine imaging.^{6,33,69,81} Patients who do not fulfill these criteria, children younger than 3 years who are involved in motor vehicle collisions or falls from more than 10 feet (especially those with axial loads to the head), and suspected victims of nonaccidental trauma should undergo radiographic evaluation of the cervical spine.^{6,82,83} Visualization of the cervicothoracic junction may necessitate the use of a swimmer's view if plain radiographs are obtained. In general, children younger than 3 are considered noncommunicative and according to Anderson et al require imaging following trauma.^{82,84} Viccellio et al performed the largest prospective randomized trial on the evaluation of pediatric cervical injuries. Use of the aforementioned criteria, outlined by the National Emergency X-Radiography Utilization Study (NEXUS), had a sensitivity and negative predictive value of 100% in ruling out pediatric cervical spine injuries.^{6,85,86} Flexion–extension plain films, CT, and MR imaging are all used adjunctively in the radiologic clearance of a pediatric cervical spine. Clearance of the cervical spine requires that both radiologic and clinical criteria be met.

Children with a neurologic deficit and suspected spinal cord injuries require CT and MR imaging evaluation. MR imaging is especially beneficial in obtunded patients with suspicious imaging and should include T2 and STIR sequences to evaluate for acute ligamentous injury and SCI.^{33,87,88} Additionally, radiographic evaluation of the remainder of the spine is recommended to avoid missed noncontiguous injuries that may not be clinically apparent because of the presence of a proximal SCI.

Firth et al found that 11.8% of children with a spinal injury had a noncontiguous fracture.⁸⁹

SSEPs and neurogenic evoked potentials are poorly studied in the pediatric trauma population. In patients with incomplete SCIs, they may have some diagnostic utility.^{69,70,90,91} Pang recommends the routine use of SSEP testing in patients with suspected SCI, especially in the setting of SCIWORA.⁷⁰ He states that SSEP testing (1) detects subtle abnormalities in the posterior column conduction pathway when the clinical examination is inconclusive, (2) helps detect SCI in head-injured children, (3) is the only feasible assessment in comatose patients or those requiring neuromuscular blockade, and (4) is occasionally useful in distinguishing between brachial plexus, intracranial, and spinal cord injuries.⁷⁰ Scarrow et al performed a pilot study in which flexion–extension plain films with concomitant SSEP testing were obtained during the clearance of cervical collars in obtunded patients.⁹² Only 1 of 15 patients studied had flexion–extension films and SSEPs that were both abnormal. This patient's MR imaging was normal, and his collar was later clinically cleared. Four additional patients had abnormal SSEPs, but the one patient with a SCI had normal SSEPs. Further study is warranted to determine the utility of SSEP testing in the pediatric population.

Concomitant vascular injury may be associated with traumatic cervical SCI. The occurrence of traumatic carotid or vertebral artery dissections in children is very low.⁹³ In the absence of penetrating injuries, CT or conventional angiography is not routinely indicated in the pediatric population.

62.7 Evidence-Based Treatment and Management

A definitive evidence-based approach to the management of pediatric SCIs does not exist. The injuries are rare, varied, and poorly studied in the literature. Nonetheless, these patients deserve high-quality care. The only way to reconcile our predicament is to use the available pediatric literature, make inferences based upon adult data, and draw from experience.

The pharmacologic treatment of spinal cord injuries, specifically the use of methylprednisolone, remains a controversial topic. The only randomized controlled trial to include children was the National Acute Spinal Cord Injury Study (NASCIS) II.⁹⁴ The results of this trial did not specifically address outcome in the group of 13- to 19-year-old patients who were 14.9 to 15.4% of each of the three treatment arms. The stratification for age and outcome was not statistically significantly different, and the results of the trial have been the subject of considerable controversy. The initial outcome measures of the study were not met, but the authors described an a priori hypothesis that greater clinical improvement could be obtained with earlier initiation of the methylprednisolone treatment protocol.⁹⁴ Bracken, the lead author of the three NASCIS trials, noted that the treatment effect of NASCIS II was relatively minor.⁹⁵ The expected motor improvement, based on Japanese, French, and American randomized controlled trials, is unilateral improvement in the motor score of 4.1 points.^{64,94–97} The score used in these trials consisted of Medical Research Council (MRC) motor grades 0 through 5 in 14 motor groups (total score, 140 per patient). According to the post hoc analysis, a patient could be expected to

have unilateral improvement of approximately one complete motor level.⁹⁵ The effect is thus not nearly as definitive as the conclusions in the original articles or in the January 2012 Cochrane Review written by the same author.^{64,94,95,98–100} The latest (2008) adult guidelines of the Consortium for Spinal Cord Medicine, an organization to which the American Association of Neurological Surgeons and Congress of Neurological Surgeons belong, do not recommend starting steroids and actually recommend stopping steroids, if they were started at another facility, as soon as possible to avoid adverse complications.¹⁰¹

Wang et al studied 30 cases of SCI in children and found methylprednisolone administration to be unrelated to neurologic improvement ($p=0.31$).¹⁰² It is important to note that only 8 children received steroids, and 5 (62.5%) had some neurologic improvement.¹⁰² The 2002 guidelines for the management of pediatric cervical spine and spinal cord injuries and the 2012 guidelines for the management of acute cervical spine and spinal cord injuries cite insufficient data to comment on steroid use in children.^{69,81} A well-powered and designed multicenter randomized controlled trial is necessary before methylprednisolone can be recommended for SCIs in the pediatric population.

Perfusion to the injured spinal cord is important during the management of acute injuries. The denervation of sympathetics, in addition to any systemic injuries sustained, may result in distributive hypovolemia, hypotension, and even neurogenic shock. Maintenance of an age-appropriate physiologic mean arterial blood pressures (MAP) is recommended in the treatment of any patient with trauma.¹⁰³ Augmentation of the blood pressure has been advocated in patients with SCI to prevent secondary injury from hypoperfusion.^{78,104–108} The two principal studies for MAP management in adults both used methylprednisolone according to the NASCIS II recommendations, thus introducing a potential confounder.^{78,109} The extent of augmentation, method of hemodynamic monitoring, and duration of treatment are not characterized in the pediatric population.

The management of pediatric SCI should include placement of an arterial line and maintenance of an age-appropriate MAP. Treatment with vasopressors to elevate the blood pressure above the mean for age and height warrants further study before definitive recommendations can be made. An appropriate course of treatment would be to maintain the MAP at the 95th percentile for age and height over a 5- to 7-day period. Based on normative data from Haque and Zaritsky, assuming that both children were in the 50th percentile for height, a 1-year-old would be maintained at an MAP of 56 mm Hg, and a 16-year-old would be managed at an MAP of 85 mm Hg.¹⁰³ The successful hemodynamic support of pediatric SCI depends on a multidisciplinary critical care team in close coordination with neurosurgery.

Operative decision making in pediatric SCI revolves around instability and spinal cord or nerve root compression. The timing of surgery is determined by the degree of instability and the presence of irreducible dislocations and incomplete injuries with or without progressive neurologic deterioration. The actual timing of decompression has been the subject of medical controversy and has far-reaching medicolegal implications. Fehlings et al demonstrated in the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) that the odds ratio for achieving an improvement of two grades on the American

Spinal Injury Association (ASIA) Impairment Scale is 2.83 (95% confidence interval, 1.10–7.28) for SCI patients undergoing decompression within 24 versus 48 hours.¹¹⁰ The study included individuals past the age of 16, and there are no studies specifically looking at early decompression in children. Dimar et al reviewed 11 articles from 1990 to 2009 comparing early and late decompression.¹¹¹ The medical literature demonstrated consistently shorter hospital and intensive care unit stays, fewer days on mechanical ventilators, fewer hospital-acquired cases of pneumonia and urinary tract infection, and no increase in operative complications with early versus late surgery.¹¹¹

62.8 Rehabilitation and Outcomes

The early involvement of a multidisciplinary team is vitally important in the care of pediatric patients with SCI because patients are surviving longer. The overall mortality rate is between 2.5 and 28%.^{4,21,89,102,112,113} The wide range of mortality rates represents sampling error due to small population size, a high rate of concurrent traumatic brain injury in certain populations, and inclusion of deaths before admission. Hamilton and Myles reported a 28% mortality rate, with 89% of deaths occurring at the scene of the accident.^{113,114} They cited a pediatric-to-adult mortality ratio of 2.5:1. The cervical spine injuries of younger children tend to be more rostral, resulting in a higher mortality rate. Children involved in motor vehicle collisions have the highest overall mortality rates and the poorest outcomes.^{21,113} Public health initiatives to keep children properly restrained in motor vehicles are vitally important, as 87% of children who died of SCI were unrestrained.¹¹³ Every illustrative case within this chapter is from a motor vehicle collision in which the child was improperly restrained.

Brown et al found that the median age for nonsurvivors was 5.3 years, with 14 of 19 children (74%) sustaining a high cervical SCI.²¹ Eleraky et al demonstrated in a similarly sized study that children younger than 10 years sustained more spinal cord and upper cervical spine injuries (► Fig. 62.4). Despite a higher

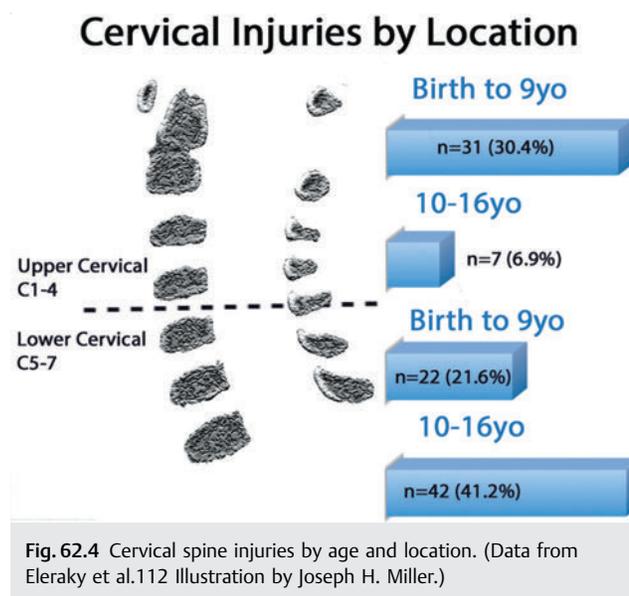


Fig. 62.4 Cervical spine injuries by age and location. (Data from Eleraky et al.¹¹² Illustration by Joseph H. Miller.)

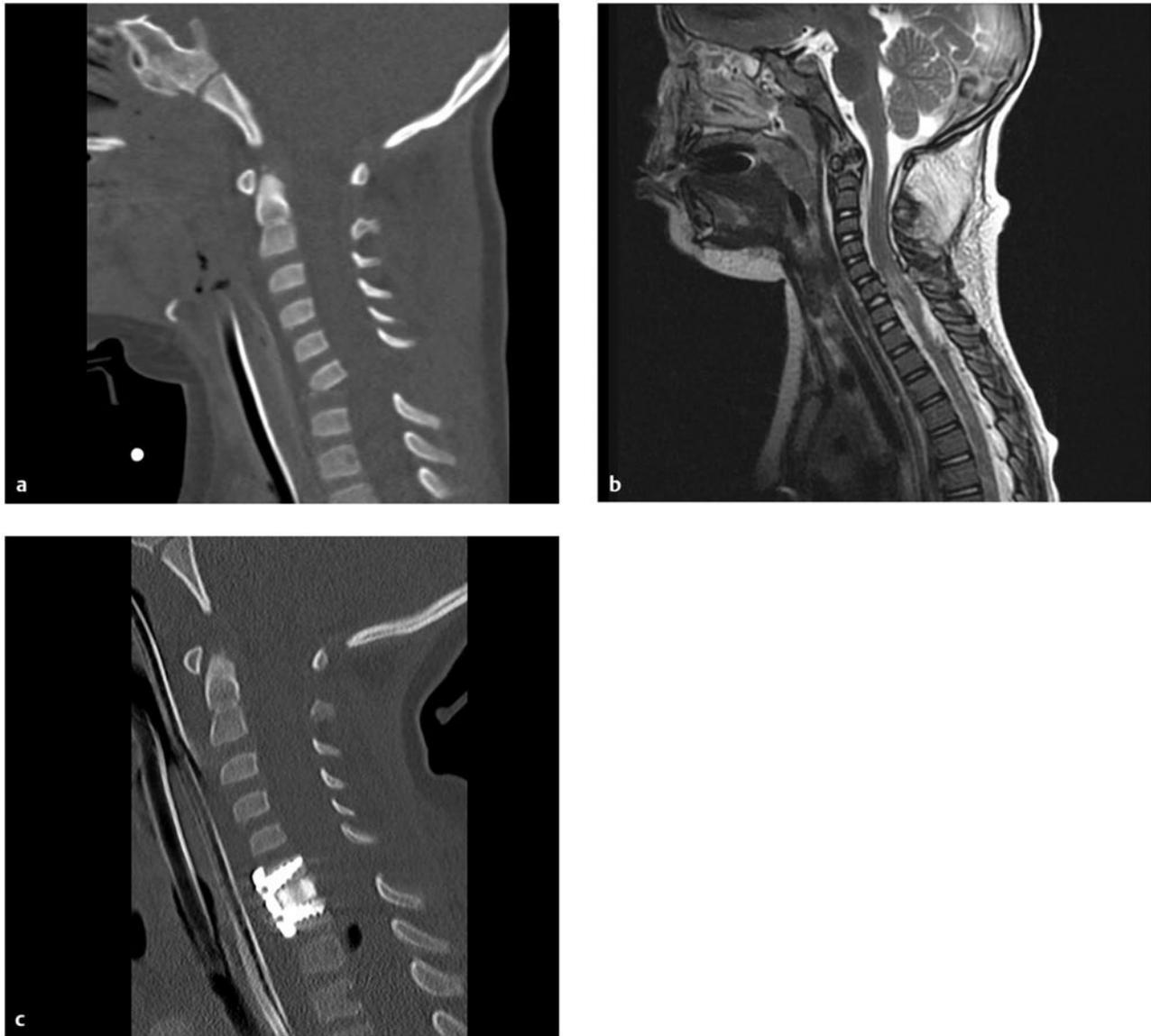


Fig. 62.5 (a,b) A 5-year-old girl after a motor vehicle collision. She initially presented with a C6 level American Spinal Injury Association (ASIA) class A injury but following anterior internal fixation/fusion (c) has improved to nearly full strength (4 + /5) in her upper extremities, including hand intrinsics. She remains weak in her lower extremities (2/5) and is unable to ambulate.

initial mortality rate than that in adults, children with SCI tend to have a more favorable long-term prognosis than adults with similar injuries.¹¹²

The NSCISC demonstrated that the life expectancy for a 10-year-old with a C5–8 cervical spine injury is 49.1 years.⁹ If that same child is ventilator-dependent, then his life expectancy is 24.1 years. The life expectancy data demonstrate that younger patients live longer because a ventilator-dependent 25-year-old has a life expectancy of only 14.9 years. Younger patients not only are living longer but also are having improved functional outcomes (► Fig. 62.5a–c).

The improvement rate of children with complete injuries (ASIA A) has been found to be as high as 35%.^{4,102} Wang et al had 20 patients who presented with complete SCI. Of these, 7 died, 7 experienced no recovery, and 6 recovered, with 5 of

them recovering to the point of ambulation.¹⁰² Factors associated with neurologic improvement were younger patient age ($p = 0.04$), SCIWORA ($p = 0.02$), and some neurologic function at presentation ($p = 0.07$).¹⁰² Eleraky et al found that in 46 patients with incomplete SCI, 38 (83%) improved completely, 3 (7%) had minimal improvement, and 5 (10%) died.¹¹² What does “minimal improvement” mean in terms of daily function? Vogel et al studied 410 adults who had experienced pediatric SCI and found that, depending on the level of injury, 28 to 39% had college degrees, 42 to 69% were employed, and 42 to 70% lived independently. Interestingly, the percentage of individuals with limited upper extremity function (C1–4 injuries) who had college degrees was higher than that in the general population. There is enormous potential for patients with pediatric SCI to live long, fruitful lives.

62.9 Complications

Short- and long-term complications that result from the initial injury or its subsequent management deserve special consideration. Pneumonia, urinary tract infections, catheter-related infections, deep vein thrombosis, pulmonary thromboembolism, and other conditions associated with prolonged hospitalization are not well characterized in the pediatric literature. These conditions are potentially preventable, as mentioned previously, with early operative intervention, and they deserve further study in children.

Complications specifically related to the spine include secondary injury, postoperative wound infections and pseudarthrosis, scoliosis, and syringomyelia. Secondary injury resulting in worsening of a neurologic injury may be prevented with appropriate prehospital immobilization, in-line or fiber-optic endotracheal intubation, and avoidance of hypotension.

The rate of postoperative complications is surprisingly low. Eleraky et al observed no complications in 30 patients and cited a 100% fusion rate.¹¹² Gluf and Brockmeyer had an 8.3% rate of wound infections, and additional studies seemed to confirm a more realistic postoperative complication rate closer to 10%.^{112,115} The risk for vertebral artery injury may be slightly higher with cervical spine screw fixation in children because the smaller lateral masses, pedicles, and pars require more precise trajectories.^{112,115} Gluf and Brockmeyer reported 2 vertebral artery injuries in 67 operative cases (1.6%).¹¹⁵ Both patients required postoperative halo immobilization, but neither had a neurologic deficit.

Instrumentation failure and pseudarthrosis are uncommon in children, but most preadolescent patients with SCI will have spinal deformity. Younger patients have a higher rate of developing scoliosis because of a lengthening torso and the adolescent growth spurt.⁸ According to Dearolf et al, scoliosis

will develop in 97% of preadolescent patients with SCI, whereas deformity will develop in only 52% of postadolescent patients.¹¹⁶ The method of initial fixation appears to be unrelated, and frequently follow-up is necessary to implement proper orthotic bracing. The rationale behind close follow-up is twofold: (1) bracing a patient before 10 degrees may prevent scoliosis and (2) bracing before 20 degrees may prevent the need for surgical correction⁸ (► Fig. 62.6).

The development of scoliosis or the delayed onset of a new neurologic development may be related to syringomyelia. Hadley et al, in a series of 122 patients, found a 4% ($n=5$) rate of syrinx development; all cases were in patients with a complete SCI.⁴ The development of a posttraumatic syrinx may be more likely with residual canal stenosis of more than 25% at the level of injury and focal kyphosis of more than 15 degrees.^{117,118} Complete decompression of the spinal cord at the time of initial operation, even in the setting of a complete injury, may prevent the development of syringomyelia.

Pearls

- The anatomical characteristics inherent to the developing spinal column place young children at increased risk for SCI.
- The early identification, immobilization, resuscitation, and treatment of acute SCI are crucial to recovery.
- Hemodynamic support and early operative decompression/stabilization are central concepts in the initial management of SCI.
- Children have better outcomes and longer survival than adults with similar injuries.

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Fig. 62.6 The aforementioned patient in ► Fig. 62.5 developed 12 degrees of levoscoliosis and was placed in a thoracolumbosacral orthosis (TLSO) brace to prevent further deformity.

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63 Intervertebral Disk Disease

Steven W. Hwang, Andrew Jea, and Thomas G. Luerssen

Intervertebral pathology of the pediatric spine is uncommonly encountered. The most frequent pathologies seen are herniated nucleus pulposus and diskitis/osteomyelitis, but other, less frequent diagnoses have been reported, such as inflammatory diskitis and conditions with neoplastic etiologies, such as chondrosarcoma and chordoma. Neoplastic conditions of the intervertebral disk space are extremely rare and are further discussed in another chapter. Pediatric disk pathology also includes adjacent processes that impact the disk space, such as spondylolysis and spondylolisthesis, which are further addressed in this chapter. Given the infrequent presentation of such pathology in children, diagnoses are often delayed, and a high index of suspicion should be raised to ensure a timely diagnosis.¹⁻³

63.1 Developmental Anatomy and Embryology

The embryogenesis of the spine has been well described.⁴ At about 4 weeks of gestation, mesenchymal cells migrate medially from the sclerotomes to surround the notochord and form the perinotochordal sheath. The sheath differentiates into alternating dense and loose areas; the loose areas become the vertebral bodies, and the dense areas become the disks. The notochord regresses completely within the vertebral bodies but persists in the disks until it ultimately undergoes mucoid degeneration to form much of the nucleus pulposus. The peripheral cells of the nucleus blend with the perinotochordal mesenchyme to form the annulus fibrosus. By the end of embryonic development (8 weeks), the distinction between the disks and bodies is clear, and notochord segmentation and formation of the annulus have begun (► Fig. 63.1). By 24 weeks, the end plates can be identified, and fibroblasts have begun to invade the nucleus.⁵

Both the annulus and the nucleus pulposus are well defined at birth. The annulus consists primarily of type 1 collagen fibrils. They are arranged in concentric lamellae that run

obliquely between adjacent vertebrae and attach to either the vertebral bodies or the cartilaginous end plates. The annulus also contains a small amount of proteoglycan and a few cells. The nucleus pulposus is composed mostly of type 2 collagen fibrils and a few cells embedded in a hydrated proteoglycan matrix. The proteoglycan molecules consist of a protein core studded with glycosaminoglycans. Chondroitin sulfate and keratin sulfate are the glycosaminoglycans most commonly found in the disk. The proteoglycan molecules can bind to hyaluronate to create large aggregates; aggrecan is the predominant form.⁶ Other collagen subtypes are found throughout the disk, but they occur in small quantities.^{6,7} Blood vessels can be found in the disk for the first several years of life. They disappear gradually and are absent by early adulthood.⁸

With normal aging, changes occur in the composition of both the nucleus and the annulus.^{6,8-10} These changes are thought to be due to the mechanical stresses imposed on the disk as well as the relatively inefficient provision of nutrients to the cells in the disk caused by the poor vascularity of the area. Over time, there is progressive dehydration of the nucleus, and degenerative granules develop in the fibrocartilage. There are areas of neovascularity and chondrocyte proliferation. Tears can be found in the annulus and the end plate. In addition, the chemical composition of the disk changes.^{6,10,11} The amount of proteoglycan in the nucleus decreases. The large aggregate molecules fragment, more keratin sulfate is present, collagen subtypes change, and inflammatory mediators can be detected. Interestingly, some of these changes can reliably be seen as early as 11 years of age.⁸ Such long-term changes explain, at least in part, the increasing incidence of disk disease associated with aging. Nevertheless, degenerative disk disease does occur in some young people.

There is growing evidence that genetic factors play a significant role in the development of disk disease. Patients with a positive family history are up to five times as likely as are those without to have a herniated lumbar disk before the age of 21 years.¹² Disease clustered in families has also been described.

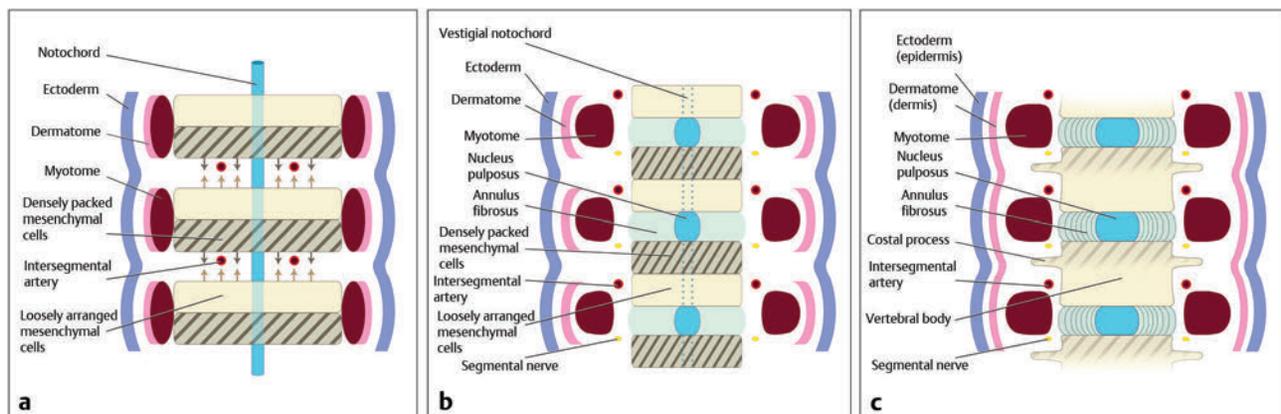


Fig. 63.1 Artist's illustration of the embryologic development of the spinal column. The somites forming the vertebral bodies divide, with adjacent rostral and caudal halves fusing to form the vertebral body and thus create the intervertebral disk space. (Printed with permission of Baylor College of Medicine.)

Scapinelli has reported eight siblings who had herniated lumbar disks; one of their parents also had disk disease. He suggested that, at least in some cases, an autosomal-dominant gene might cause disk herniation.¹³ Animal studies support this notion. Transgenic mice with mutations of the genes that produce either type 9 collagen or aggrecan have an extremely high incidence of disk disease.^{14,15} Similar findings have been reported in humans. For example, two Finnish studies reported variations in the collagen 9 alleles of persons with and without disk degeneration.^{16,17} Kawaguchi et al have described aggrecan abnormalities in patients with multilevel disk degeneration.^{18,19} In addition, variations in the gene coding for vitamin D receptor and matrix metalloproteinase 3 have been linked to disk degeneration.^{20–23}

63.2 Degenerative Disk Disease

Disk herniation is usually a pathologic process associated with degenerative disease and is assumed to be multifactorial, influenced by environmental and genetic factors.²⁴ Disk herniation also occurs in the pediatric population, but the incidence is much lower than in adults.¹ The number of cases requiring surgical treatment is 5.5 per 100,000 person-years in the population less than 25 years old, compared with 128 cases per 100,000 person-years in the 40- to 45-year-old age group.²⁵

63.2.1 Clinical Presentation

The clinical presentation of lumbar disk herniation in children is similar to that described in adults; common symptoms, in up to 50% of patients, include lumbar radiculopathy out of proportion to low back pain and motor and/or sensory loss^{1,26–30} (► Fig. 63.2). However, it is not clear that the findings in adult disk herniation can be applied to a similar management strategy in the pediatric population because the structural properties of disks and environmental exposures differ between children and adults.^{1,31}

63.2.2 Treatment

Recent reports have indicated that cohorts of adult patients who undergo surgical or conservative treatment for lumbar

disk herniation exhibit similar long-term outcomes, but the outcome is unknown in children because the treatment has not been studied in the pediatric age group.³² In the largest series of pediatric patients undergoing lumbar microdiscectomy to date, Cahill et al¹ noted that although pediatric patients may not respond as well to conservative treatment as adults do, a significant proportion of them still do respond; therefore, one should attempt conservative therapy before considering surgery unless neurologic motor deficits require a more urgent operation. There have been limited reports of case series encompassing traditional open discectomy and modern microdiscectomy in pediatric patients.^{1,28–30,33,34}

Our small case series of six children³⁵ indicates that minimally invasive surgery for lumbar disk herniation in the pediatric population is a safe and efficacious procedure. The average blood loss was minimal, and the majority of patients were discharged home on the same day as surgery or the first postoperative day. The lumbar incision is about 22 mm in length, a reported cosmetic benefit. Patients are usually mobile several hours after surgery, although we limit strenuous physical activity for 12 weeks. Athletes were able to return to competitive sports after this period of activity restriction. In our series, there were no postoperative complications, including cerebrospinal fluid leak or recurrence of disk herniation; however, this may be due to the small number of patients who have undergone minimally invasive surgery and our lack of long-term follow-up.

Although there were no complications in our pediatric series, early postoperative complications reported by others in the literature include wound hematoma (1 to 4%) and delayed wound healing (3%).^{26,32,35} Postoperative infection, such as wound infection and diskitis secondary to lumbar spine surgery, is rare in children and adolescents.^{29,36,37} There have also been reports of narrowing of the disk space, foraminal stenosis, and adjacent disk degeneration after discectomy in the pediatric population, similar to results found in the adult population.^{27,37–40} Moreover, the rate of reoperation can be as high as 24% after extended follow-up.^{26,33,41}

63.3 Traumatic Disk Disease

Posterior vertebral rim fracture, a fracture of bone fragments at the posterior rim of the vertebral end plate with an associated



Fig. 63.2 (a) Midsagittal and (b) axial magnetic resonance images of the lumbosacral spine show a central disk herniation at L5–S1 associated with a “black” degenerated disk.



Fig. 63.3 (a) Midsagittal computed tomographic scan of the lumbosacral spine shows an L1–L2 apophyseal ring fracture associated with disk herniation. (b) Midsagittal and (c) axial T2-weighted magnetic resonance images of the lumbosacral spine demonstrate L1–L2 disk herniation and significant lumbar canal stenosis.

disk herniation, has been given several names: posterior marginal node; limbus fracture; fracture of the vertebral rim, ring, or end plate; epiphyseal dislocation; and apophyseal ring fracture^{42–49} (► Fig. 63.3). The mechanism of vertebral end plate fractures is not completely known. However, most authors have postulated that the pathogenesis of these fractures is trauma or strenuous physical activity.

63.3.1 Clinical Presentation

Young patients may present with a back injury⁵⁰ associated with disk herniation. The intervertebral disk is attached to the end plate by Sharpey fibers, and the end plate is separated from the remainder of the vertebral body by a cartilaginous growth plate that is replaced by bone only at 18 to 25 years of age. After the apophyseal ring of the end plate ossifies in the immature spine (typically between the ages of 10 and 15 years), this cartilaginous junction is relatively weak and susceptible to compressive and tension stresses.^{51,52} Disk herniation through the cartilaginous plate and fracture or fragmentation of the ring apophysis can occur together in response to shearing or recurrent stress.^{53,54}

Conventional X-rays and/or computed tomography (CT) may define the bone fragment, associated disk herniation, vertebral defect, and the severity of underlying spinal stenosis.^{53,55,56} Magnetic resonance (MR) imaging may also show the avulsed fragment and a defect in the posterior vertebral rim. Associated disk degeneration and herniation are usually present, and the spinal canal may be stenotic.^{54,55,57} The Epstein classification⁵⁵ of posterior vertebral rim fractures, although seldom applied, demonstrates the range of radiographic appearances of these injuries. Type I fractures are simple avulsions of the posterior cortex of the end plate; they are so thin that no obvious defect is present in the vertebral body, although an arcuate fracture fragment is visible. Type II fractures are similar in position but include medullary bone and a defect in the vertebral body. Type III fractures are small and lateral. Type IV fractures run the full height of the vertebral body and extend to both vertebral end plates^{50,55} (► Fig. 63.4).

The differential diagnosis includes ossification of the posterior longitudinal ligament, disk calcification, osteophyte formation, and disk herniation. The most important diagnostic features are the vertebral defect and the bone fragment.

This condition usually affects patients in adolescence and early adulthood, with a male-to-female ratio of 2:1.⁵⁵ The true incidence of end plate fractures associated with disk herniation

remains unknown, but the condition is increasingly becoming recognized.⁵⁸ Vertebral rim fractures may be asymptomatic. Symptomatic patients may initially present with back and leg pain, reduced lumbar movements, and restricted straight leg raise, similar to adolescents with disk herniation; motor and bowel and bladder dysfunction are usually late findings.^{53,55,56} Older adult patients may present with neurogenic claudication due to pre- or coexisting lumbar stenosis.⁵⁵

63.3.2 Treatment

Not all patients with a posterior vertebral rim fracture require surgery. In a series of 21 patients,⁵⁹ 57% responded well to conservative treatment. However, if a patient has symptoms of radiculopathy or neurogenic claudication, the treatment of choice has been discectomy with removal of the fracture fragments.^{42,55} In this case, the standard discectomy exposure may not allow adequate removal of the fracture fragments or decompression of the spinal canal, increasing the risk of surgery. Based on our experience, we advocate simple decompressive laminectomy alone to treat pediatric patients who have

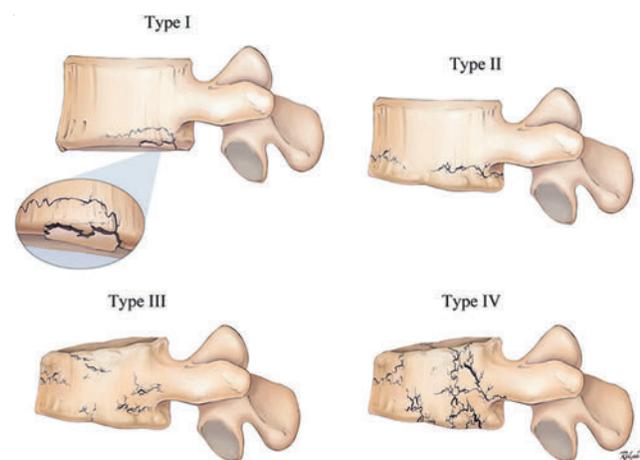


Fig. 63.4 The Epstein classification of posterior vertebral rim fractures. Type I fractures are simple avulsions of the posterior cortex of the end plate—so thin that no obvious defect is present in the vertebral body, although an arcuate fracture fragment is visible. Type II fractures are similar in position but include medullary bone and a defect in the vertebral body. Type III fractures are small and lateral. Type IV fractures run the full height of the vertebral body and extend to both vertebral end plates.

neurogenic claudication associated with posterior vertebral rim fractures. Our patients experienced good relief of preoperative symptoms and a satisfactory functional outcome. Overly aggressive laminectomy that weakens the pars interarticularis and subsequently destabilizes the vertebral column should be avoided.

63.4 Inflammatory Disk Disease

Pediatric idiopathic/ inflammatory intervertebral disk calcification is an uncommon entity. It affects the intervertebral disks and adjacent vertebral body and musculoligamentous structures, resulting in local pain or sensorimotor disturbances.⁶⁰ The etiology of pediatric idiopathic/inflammatory intervertebral disk calcifications is unknown, although associated fever, pain, and stiffness suggest an inflammatory condition. The clinical course is usually benign and self-limited, with the fever and pain resolving spontaneously within weeks or months^{61–71}; calcification of the disk space is seen at the end of the inflammatory phase.

63.4.1 Clinical Presentation

A recent review⁷² of pediatric idiopathic/inflammatory intervertebral disk calcification found a male predominance (male-to-female ratio of 8:5). Most patients are between 5 and 12 years of age. The lower cervical spine is most frequently affected, with 50% of the cases of intervertebral disk calcification occurring in the cervical spine.⁶⁵ In particular, almost all patients with cervical lesions (99.8%) are symptomatic, whereas all patients with lumbar lesions are asymptomatic.

Abnormal levels of inflammatory markers are found in half of the patients who undergo laboratory examination. The erythrocyte sedimentation rate (ESR) is the most sensitive indicator, elevated in more than 90% of patients. Considering also that more than 70% of symptomatic patients had muscle pain, an inflammatory etiology for pediatric idiopathic/inflammatory intervertebral disk calcification seems likely.

63.4.2 Treatment

In a review of the literature with more than 300 reported cases of pediatric idiopathic/inflammatory intervertebral disk calcification, only 7 patients were treated with surgery.^{71,73–77} Most surgically treated patients had a good outcome except for 1 patient with a permanent neurologic deficit.⁷⁵ On the other hand, all patients who were treated conservatively showed good functional outcome. Neither the surgical indication nor the purpose of surgery has been established in the treatment of pediatric idiopathic/inflammatory intervertebral disk calcification. Nerve root or spinal cord compression by a calcified disk may not be considered an absolute indication for surgical intervention.⁷⁸ Conservative management seems to be the mainstay of the treatment for pediatric idiopathic/inflammatory intervertebral disk calcification except in the uncommon patients presenting with acutely progressive and severe neurologic deficits.⁶⁰

63.5 Spondylodiskitis/ Osteomyelitis

Pathogens commonly encountered in children include *Staphylococcus aureus*, followed by *Streptococcus pneumoniae* and *Salmonella* species.^{2,79} Although various hypotheses of trauma and inflammation have been proposed, disk space infection is commonly thought to arise from infection at a prior site that has spread via three possible routes: hematogenously, by direct inoculation, or by direct extension. Almost 50% of children will have had a prodromal illness related to their disk space infection,⁸⁰ and immunosuppression is a reported risk factor. In children, blood vessels are present in the annulus fibrosus, and the vessels within the vertebral body typically are anastomotic, but as in adults, there are no vessels or lymphatics within the nucleus pulposus. These anatomical variations have been proposed as a reason for the preferential localization of bacterial infections to the intervertebral disk space.

Spondylodiskitis is less commonly encountered in children than in adults and has a bimodal distribution (0 to 2 years and older than 10 years). It affects mainly the thoracic and lumbar spine.^{79–81} Diagnosis can often be delayed up to 4 to 6 months as a consequence of the low incidence and vague presentation in children.^{2,3} Most commonly, children present with back pain, but nonspecific symptoms are often the only presentation, frequently without fevers. Very young children with diskitis often may refuse to walk, show regression of ambulatory motor skills, display the Gowers sign, or refuse to sit.^{82,83} Several authors have proposed categories of symptoms for children presenting with diskitis: back pain, hip and leg pain, meningeal symptoms, abdominal symptoms, and “irritable child” syndrome.^{81,84} If epidural extension is present, children may present with neurologic compromise as well.

Laboratory values (complete blood cell count, ESR, C-reactive protein [CRP]) and blood cultures should be routinely obtained, but they are often normal or only mildly elevated.⁸⁰ Blood cultures will often be positive early in the course of the illness, but given the delay in diagnosis, often only 50% are diagnostic. Very early in the course, plain radiographs may be negative because it typically takes 2 weeks to a month before disk space narrowing becomes apparent.³ The initial evaluation should include MR imaging of the entire spine with contrast. Both MR images and bone scans will reveal the abnormality, but MR imaging generally demonstrates the problem somewhat earlier.⁸⁵ Technetium 99 bone scans will identify the problem 7 to 12 days after the onset of symptoms but are nonspecific, and distinction between inflammatory and neoplastic processes is required.^{86,87} Given the vascular supply in the pediatric spine, bacterial infections typically involve the disk space, and the isocenter of the infection can often be localized to the intervertebral disk space. If the disk spaces appear relatively preserved or uninvolved, concern for tuberculous infection should be raised⁸⁸ (► Fig. 63.5).

In the pediatric population, the treatment is controversial because most spondylodiskitis infections have a relatively benign course. If a pathogen is not identified, a CT-guided biopsy should be considered before the initiation of antibiotic treatment unless clinically contraindicated (declining or unstable

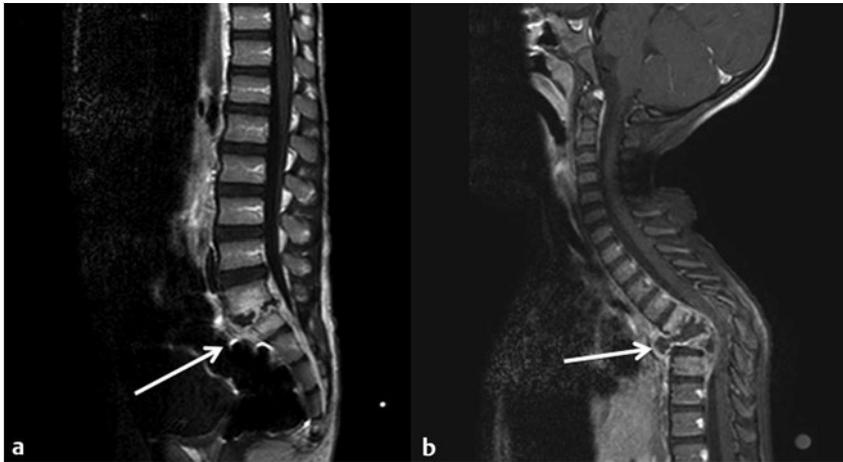


Fig. 63.5 (a) Sagittal postcontrast magnetic resonance (MR) image of the lumbar spine showing a pyogenic infection centered at the disk space with epidural extension (*white arrow*). (b) Sagittal postcontrast MR image of the thoracic spine of a patient with a tuberculous infection shows relative preservation of the adjacent disk spaces but significant involvement of the vertebral bodies (*white arrow*).

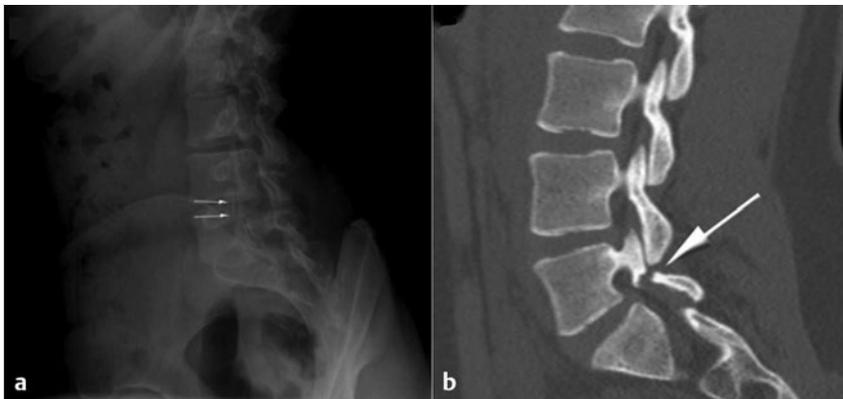


Fig. 63.6 (a) Oblique lumbar radiograph showing the pars defect (arrows) across the neck of the "Scottie dog." (b) Sagittal computed tomographic scan showing the pars defect highlighted by the *arrow*.

clinical condition). However, given the self-limiting and indolent course of the infection in children, this is also controversial; many authors will treat an infection empirically and biopsy only a refractory case. Some authors advocate no treatment with observation only because the course is often self-limiting.^{89,90} More routinely, however, a course of intravenous antibiotics followed by oral antibiotics for 6 to 8 weeks is prescribed. Given the relatively high incidence of vertebral body wedging and loss of disk space height, the adjuvant use of immobilization through a cast or brace has been proposed by some authors. Surgery can also be considered for patients with refractory and progressive infections not responding to antibiotics, but those with nondiagnostic biopsies can typically be treated with broad-spectrum antibiotics for the duration of therapy. Epidural extension with neurologic compromise should be treated with emergent decompression and evacuation of the infection.

Given the usually self-limited course, outcomes for this pathologic entity are excellent.^{79,80} Kayser et al reported 10-year or longer follow-up in 20 children and noted that 80% had no symptoms with a "freely mobile spine," whereas the remaining 20% had focal kyphosis and some restriction of spinal movement. All patients had radiographic narrowing of the disk space, and 40% had some degree of fusion across vertebrae.⁷⁹

The reported indolent and self-limiting course, as well as the high incidence of nondiagnostic blood cultures and CT-guided biopsies, may be partially due to the inclusion of nonpyogenic infections. An entity known as chronic recurrent multifocal

osteomyelitis (CRMO) or nonbacterial osteomyelitis (NBO) should be distinguished from spondylodiskitis/osteomyelitis. It is often associated with a syndrome of SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis).⁹¹ Typically, CRMO is multifocal. Patients are often healthy between episodes, with symptoms extending beyond 6 months.^{92–94} Young girls between the ages of 4 and 14 years are more often affected (5:1), but the etiology is poorly understood.^{95,96} Most patients have palmoplantar pustulosis or psoriasis. Patients may have minor diagnostic criteria of normal or mildly elevated laboratory values (CRP, ESR), hyperostosis, other autoimmune diseases, and an associated family history. Radiographic images can mimic those of osteomyelitis, but other long bones are typically involved, such as the clavicle. Bone biopsies are sterile but demonstrate evidence of inflammation and/or sclerosis or fibrosis.⁹² Standard therapy involves the use of nonsteroidal anti-inflammatory drugs, but alternate medications, such as oral steroids, methotrexate, and bisphosphonates, have been reported with positive early results.^{97–100}

63.6 Spondylolysis

Spondylolysis is to an abnormality in the pars interarticularis that is typically due to a stress or fatigue fracture. It is classified into five categories based on the presumed etiology: dysplastic, isthmic, degenerative, traumatic, and pathologic.¹⁰¹

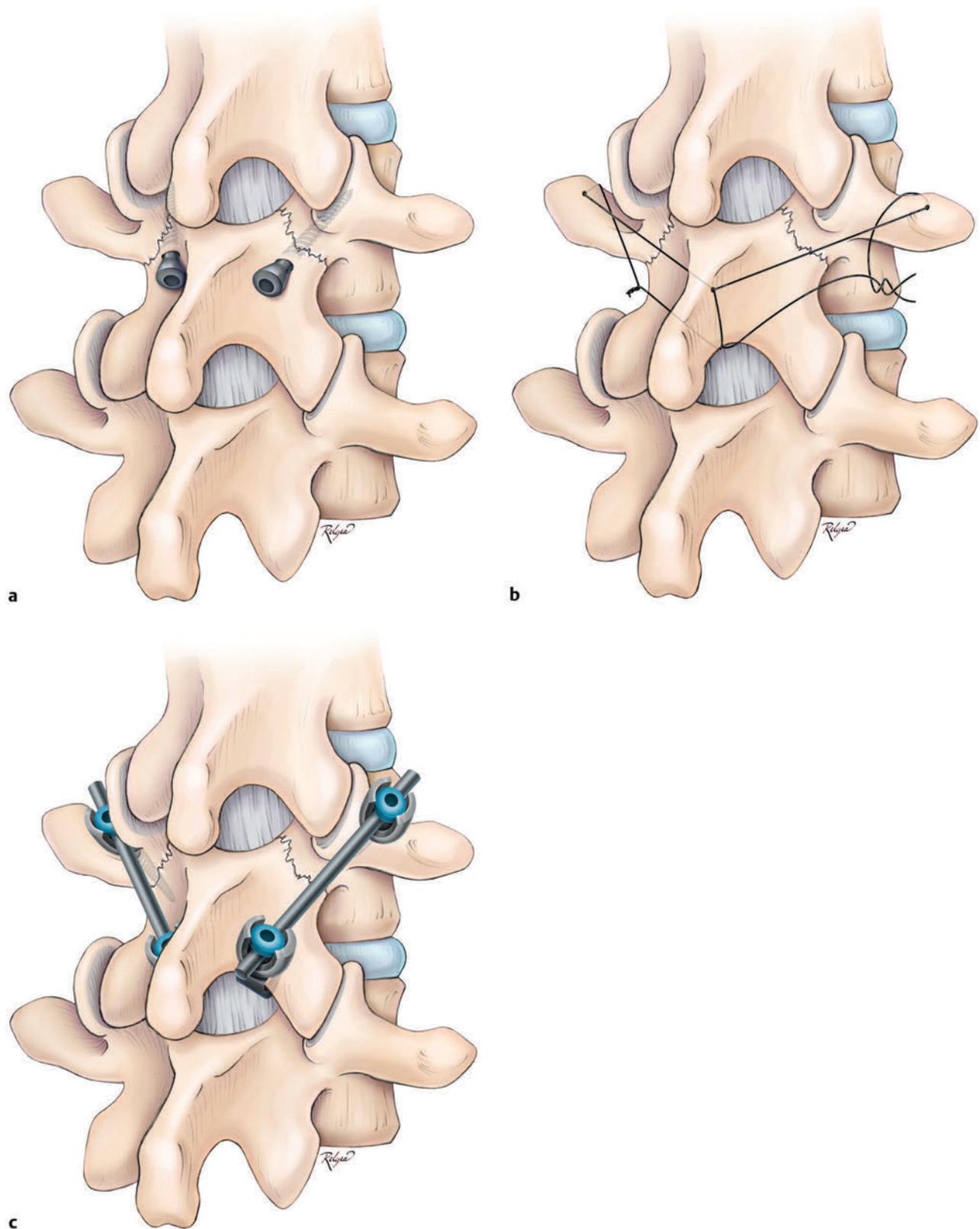


Fig. 63.7 Artist's illustration of various surgical techniques for spondylolytic repair. (a) Direct pars screw. (b) Scott's technique of wiring. (c) Laminar hook and pedicle screw construct. (Printed with permission of Baylor College of Medicine.)

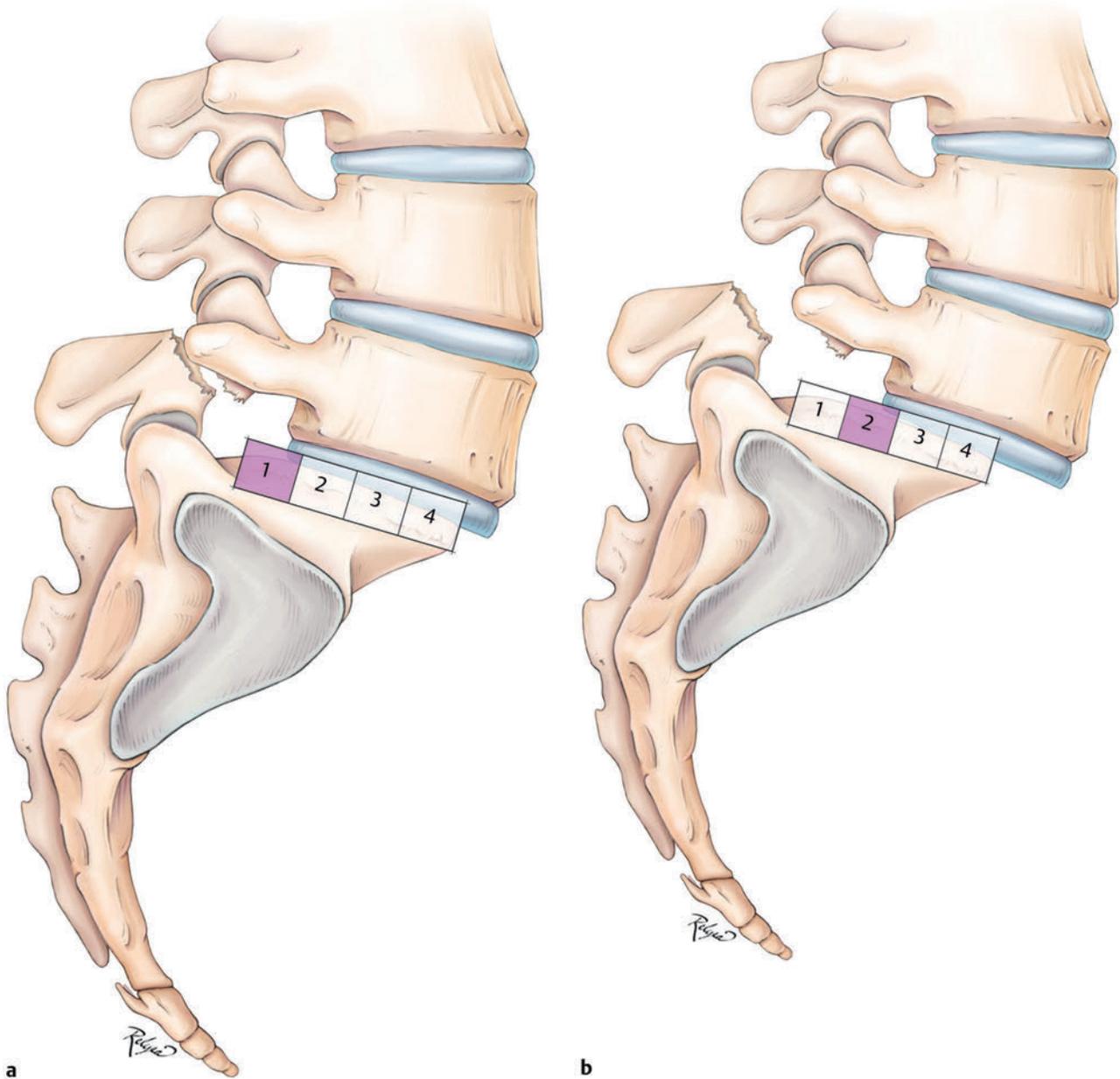


Fig. 63.8 Artist's illustration highlighting the various grades of spondylolisthesis: (a) grade 1, 0 to 25%; (b) grade 2, 26 to 50%. (Printed with permission of Baylor College of Medicine.) (continued)

The dysplastic and isthmic subtypes are most often represented in the pediatric population; dysplastic types are often associated with other osseous abnormalities and an elongated pars interarticularis, whereas isthmic subtypes are due to repeated trauma. The natural history is poorly understood, but it is generally thought to be nonprogressive. Fredrickson et al reported an incidence of 4.4% in asymptomatic schoolchildren at 6 years of age, which increased to 6% by 18 years of age.¹⁰² The increasing incidence may be related to mechanical motion and repeated stresses accrued with age. Increasing forces loaded onto the facets with hyperextension movements of the spine are believed to contribute to the development of spondylolysis. An increasing incidence (up to 47%) of spondylol-

ysis among participants in elite athletic activities such as gymnastics, tennis, diving, and weight lifting has been reported.¹⁰³⁻¹⁰⁵ Furthermore, a hereditary predisposition appears to contribute to a higher frequency among family members, but specific genes have not been identified.^{106,107}

Patients often present with low back pain after exacerbation with activity that does not resolve in an appropriate time frame. As the pathology progresses, focal hypertrophy of the synovium or an inflammatory reaction at the pars defect can develop that may extend to involve the adjacent nerve root, causing radiculopathic symptoms or signs. Patients may also have associated spondylolisthesis that may progress, further contributing to back pain.

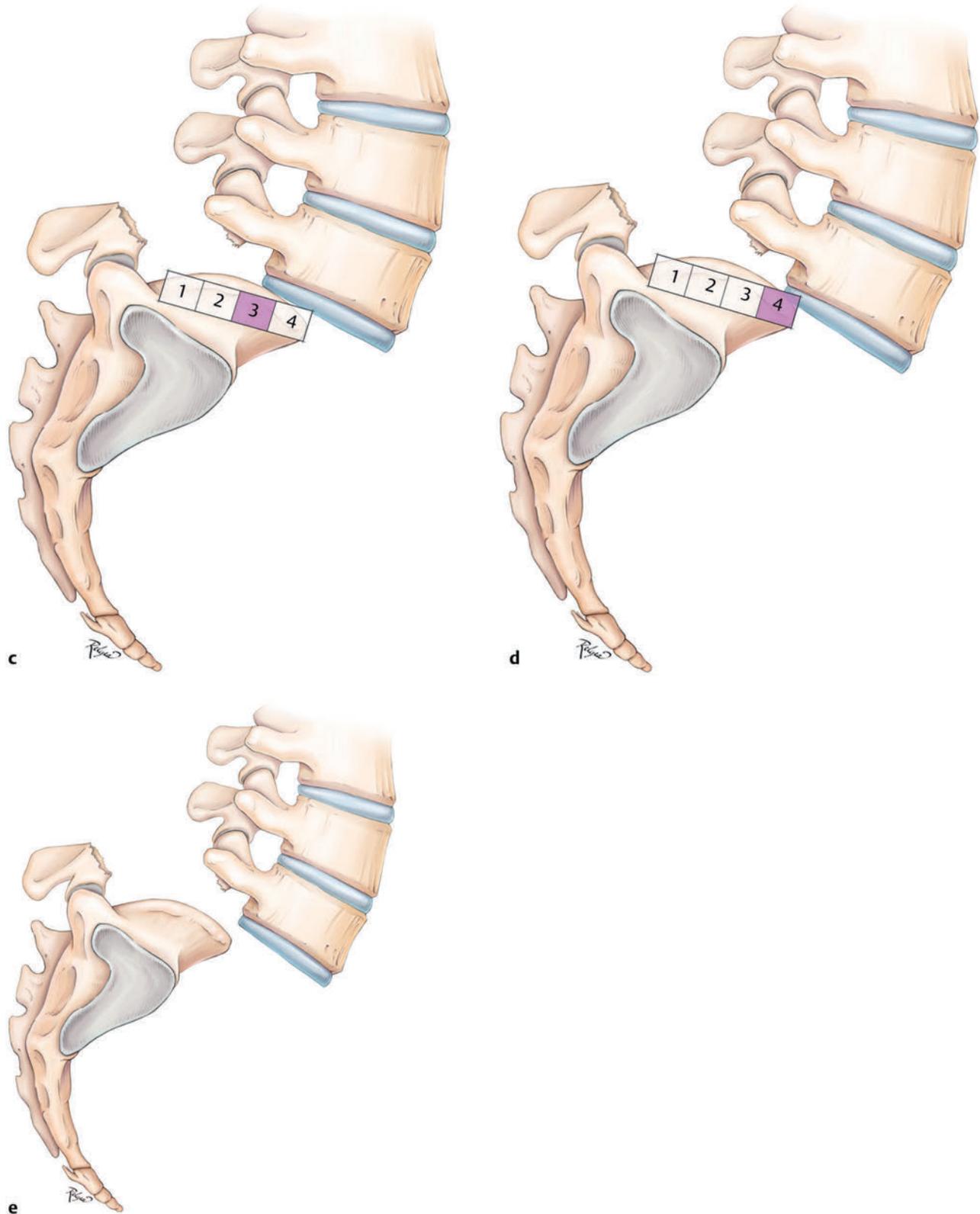


Fig. 63.8 (continued) (c) grade 3, 51 to 75%; (d) grade 4, 76 to 100%; (e) spondyloptosis, >100%.

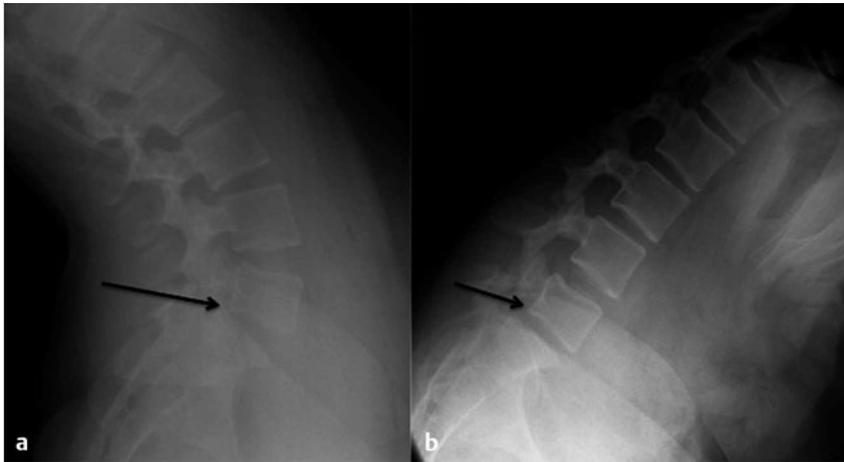


Fig. 63.9 Upright lateral lumbar radiographs showing increased movement of the vertebral bodies with (a,b) extension and flexion. The black arrows highlight the grade 1 spondylolisthesis at L5-S1.

The radiographic evaluation of a patient thought to have spondylolysis should begin with anteroposterior, lateral, and oblique radiographs (► Fig. 63.6). If only anteroposterior and lateral films are obtained, approximately 20% of defects are missed. The classic description of spondylolysis is that of La Chapelle—a radiolucency in the neck of a Scottish terrier (“Scottie dog sign”) seen on oblique views. If plain radiographs are nondiagnostic, CT of the lumbar spine is routinely then performed, followed by a bone scan. If the patient’s symptoms are long-standing (longer than 1 year), a bone scan is less likely to be useful. Read recommends single proton emission computed tomography (SPECT) for adolescents suspected of having spondylolysis because of this technique’s superior resolution and sensitivity.¹⁰⁸

Lesions that are detected early may be more responsive to nonoperative therapy, such as immobilization and rest. Particularly in the presence of stress fractures of the pars interarticularis without cortical break, early immobilization with a thoracolumbosacral orthotic (TLSO) brace with or without a hip extension has shown better results than rest alone.^{109,110} The brace is usually worn for 6 to 12 weeks until the pain resolves, and that treatment is followed by a course of physical therapy and gradual return to activity. With failed conservative therapy, several surgical options are available. Various techniques include a direct pars screw, wiring of the lamina to the spinous processes, and the construct of a laminar hook and pedicle screw connected with a rod^{111–113} (► Fig. 63.7). These techniques all bridge the pars defect and apply a compressive force across the pars with successful outcomes and fusion rates up to 100%.¹¹² Although most cases are successfully treated conservatively, excellent outcomes can be achieved for patients requiring surgical intervention.

63.7 Spondylolisthesis

Spondylolisthesis typically occurs in the setting of bilateral pars defects and appears as anterior displacement of one vertebral body on another (typically L5 on S1). It has typically been classified with the Meyerding system, in which overlap of each quarter of the vertebral body is denoted as 1 grade (i.e., 0 to 25% overlap, grade 1; 26 to 50% overlap, grade 2; etc.).¹¹⁴ Complete overhang of one vertebra over the adjacent level is termed *spondyloptosis* (► Fig. 63.8).

Patients typically present with low back pain. With severe spondylolisthesis, there may be radicular symptoms from foraminal stenosis, although compression of the cauda equina is uncommon because the posterior elements are often noncontiguous with the vertebral body. With higher-grade spondylolistheses, patients will often have increased lumbar lordosis and hamstring contractures secondary to sacropelvic parameters. Patients with severe spondylolisthesis often have a larger sacral slope (angulation between the end plate of S1 and a horizontal line) that correlates with increased lumbar lordosis. Typically, spondylolisthesis is easily seen on lateral radiographs, and the slip is often accentuated with flexion and extension views (► Fig. 63.9).

Conservative measures, such as brace immobilization and physical therapy, can be used with good outcomes for patients presenting solely with back pain and no significant instability on dynamic radiographs. Low-grade slips rarely progress over time, and most patients respond to conservative therapy.^{115–117} However, symptomatic high-grade spondylolistheses respond less well to conservative therapy, and dysplastic spondylolysis carries a greater risk for progressive olisthesis over time. Therefore, many surgeons advocate surgical management of these patients.^{118–120} In the setting of significant dynamic movement, neurologic compromise, or failed conservative therapy, surgery is necessary. Surgical intervention varies from in situ fusion to instrumented fusion with or without reduction of the spondylolisthesis (decompressive Gill procedure, transforaminal interbody fusion, posterior lateral fusion, anterior fusion, circumferential fusion, Bohlman dowel, or Gaines two-stage procedure). Typically, an attempt is made to reduce symptomatic high-grade spondylolistheses (grades 3 and 4) to restore sagittal balance and improve a high slip angle, thereby theoretically preserving function and sacropelvic parameters while minimizing the incidence of pseudarthrosis. However, management remains controversial, and even in patients with high-grade spondylolistheses, in situ fusion with postoperative bracing or casting has had comparable long-term outcomes in some series.¹²¹ The surgical reduction of high-grade slips has a higher associated complication rate, particularly with respect to pseudarthrosis and nerve root injury.¹²²

Symptomatic relief and fusion rates from approximately 70 to 100% have been reported with in situ fusion.^{118,123–125} With the use of instrumented fusion, circumferential stabilization

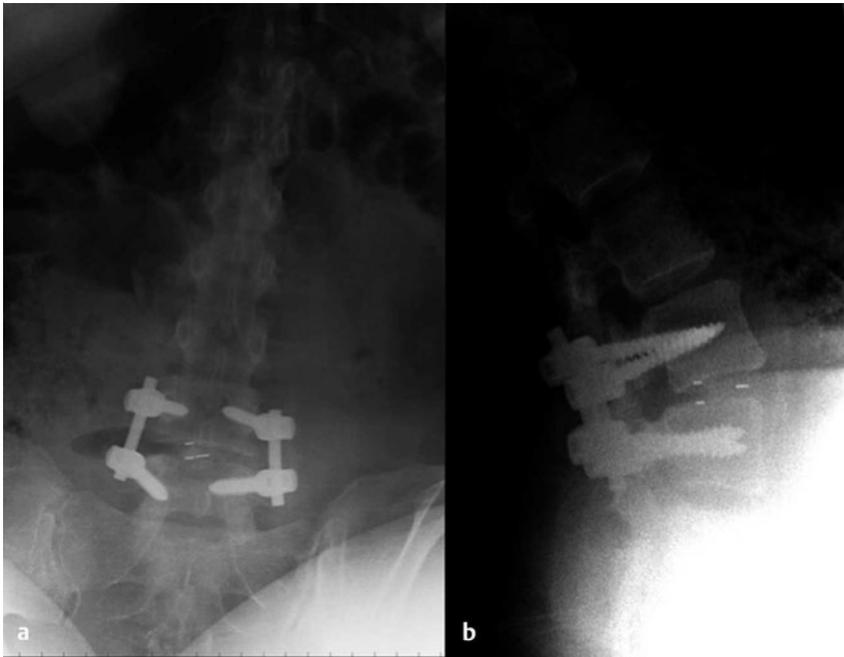


Fig. 63.10 (a,b) Postoperative radiographs showing reduction of a spondylolisthesis from a transforaminal interbody fusion (TLIF).

(anterior/posterior) has resulted in improved long-term clinical and radiographic outcomes in some series.¹²⁶ However, comparative outcomes for circumferential fusion from a posterior approach alone (transforaminal interbody fusion/posterior lumbar interbody fusion [TLIF/PLIF]) have not been well defined in the pediatric population (► Fig. 63.10).

63.8 Conclusion

Pediatric intervertebral disk pathology is uncommon. The most frequently encountered pediatric intervertebral disk pathology is herniated nucleus pulposus, which is typically seen in teenagers as they approach adulthood. Intradiskal pathology in younger children is even more uncommon. Therefore, it is difficult to determine optimal treatment algorithms in this population, given the paucity of cases reported. Management guidelines are generally extrapolated from the adult literature and may not fully apply to younger patients. Multicenter collaborations are required to help address these limitations in our understanding of such uncommon pathologic entities.

Pearls

- Intervertebral disk pathology is uncommon in children, and the diagnosis of such pathology is often delayed because of nonspecific presentations. A high index of suspicion is required to confirm many of these diagnoses.
- MR imaging is the most useful imaging modality to confirm the presence of pathology and to help distinguish among various etiologies, but it is still difficult to differentiate infection from nonpyogenic diskitis.
- The treatment algorithms for most forms of pediatric intervertebral disk disease are based on adult experience, but significant differences may exist that require further investigation for better elucidation.

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64 Cavernous and Venous Malformations

Edward R. Smith and R. Michael Scott

Vascular malformations of the central nervous system (CNS) are a heterogeneous group of lesions that occur in both the brain and spinal cord. Like those in other anatomical sites, CNS vascular anomalies can be classified according to rheologic characteristics (fast-flow and slow-flow) and by channel composition (i.e., arteriovenous malformation, capillary malformation, and venous malformation) and may occur either independently or in association with syndromic conditions.

Cerebral cavernous malformation (CM) consists of compact clusters of spongelike vascular spaces without intervening neural parenchyma. The nomenclature for these malformations can be confusing as they have been called cavernomas, cavernous angiomas, and cavernous hemangiomas. *Venous malformation (VM)* is a confluent collection of enlarged veins. *Developmental venous anomaly (DVA)* is a collection of small veins converging into a dilated venous trunk. *Capillary malformation*, usually termed *capillary telangiectasia*, is usually found within the substance of the brain, especially the pons or basal ganglia; it consists of an unencapsulated collection of enlarged capillaries.

The focus of this chapter rests on CM, as the true venous malformations (DVA, VM, capillary telangiectasia) are not generally pathologic or causative of disease and, as a rule, should not be treated, although in certain circumstances they may cause headache or seizure disorders. In contrast, CMs can affect children through hemorrhage, seizure, focal neurologic deficits, and headache.

64.1 Pathology

Pathologically, CMs are a compact mass of sinusoidal vessels contiguous with one another without intervening normal

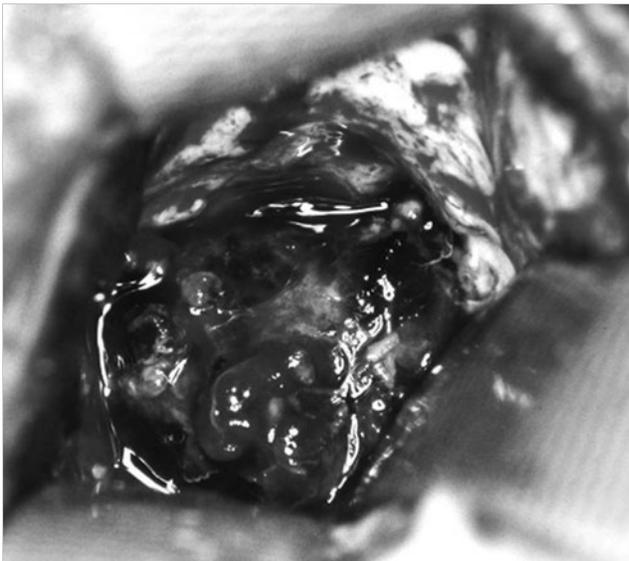


Fig. 64.1 A cavernous malformation in situ following corticectomy and linear craniotomy. The lobulated varices contain clotted and flowing blood, and the adjacent white matter is stained orange from hemosiderin from previous hemorrhages.

parenchyma. These well-circumscribed, unencapsulated masses are identified grossly as having a purple, lobulated, “mulberry” appearance (► Fig. 64.1). Calcifications may be present, both grossly and microscopically (► Fig. 64.2). Cysts containing old hemorrhage products may be present and may help explain the controversial phenomenon of growth of these lesions, providing a substrate for neovascularization following hemorrhage. Adjacent brain may be gliotic, contain focal calcifications, and frequently is stained with hemosiderin from prior hemorrhage.

64.2 Epidemiology

Most cases are sporadic (50 to 80%), although familial variants exist, with most familial cases demonstrating multiple lesions on imaging.^{1,2} Very few (approximately 10%) sporadic cases will have multiple lesions. Multiple CMs can also be found in association with cranial irradiation.^{1,3-5} CMs are found with a prevalence of about 0.5% in autopsy studies.^{1,2,6,7} A diagnostic incidence of 0.43 per 100,000 people per year has been reported.⁸ There is no difference in sex incidence.

64.3 Presentation

CMs can cause symptoms of hemorrhage or progressive enlargement with mass effect. Symptoms often depend on the location of the lesion within the CNS and can include headache, seizure, and focal neurologic deficit.⁹⁻¹² Seizure is the presenting symptom in 25 to 30% of cases. However, many CMs are asymptomatic and are frequently found incidentally.

64.4 Radiographic Evaluation

Initial studies that reveal CM usually consist of computed tomography (CT) or magnetic resonance (MR) imaging (► Fig. 64.3,

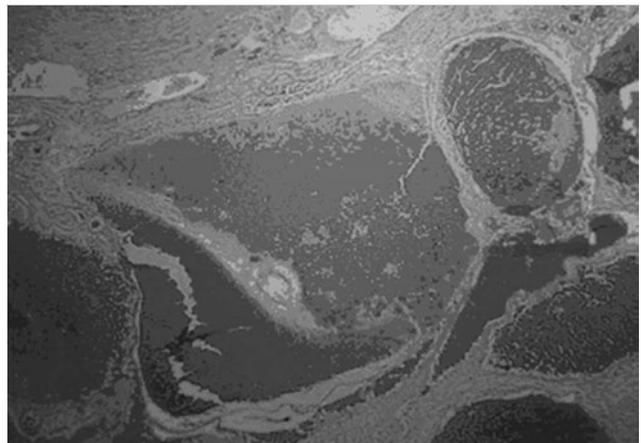


Fig. 64.2 Microscopic appearance of a typical cavernous malformation demonstrating thin-walled endothelial channels with little or no intervening brain tissue.

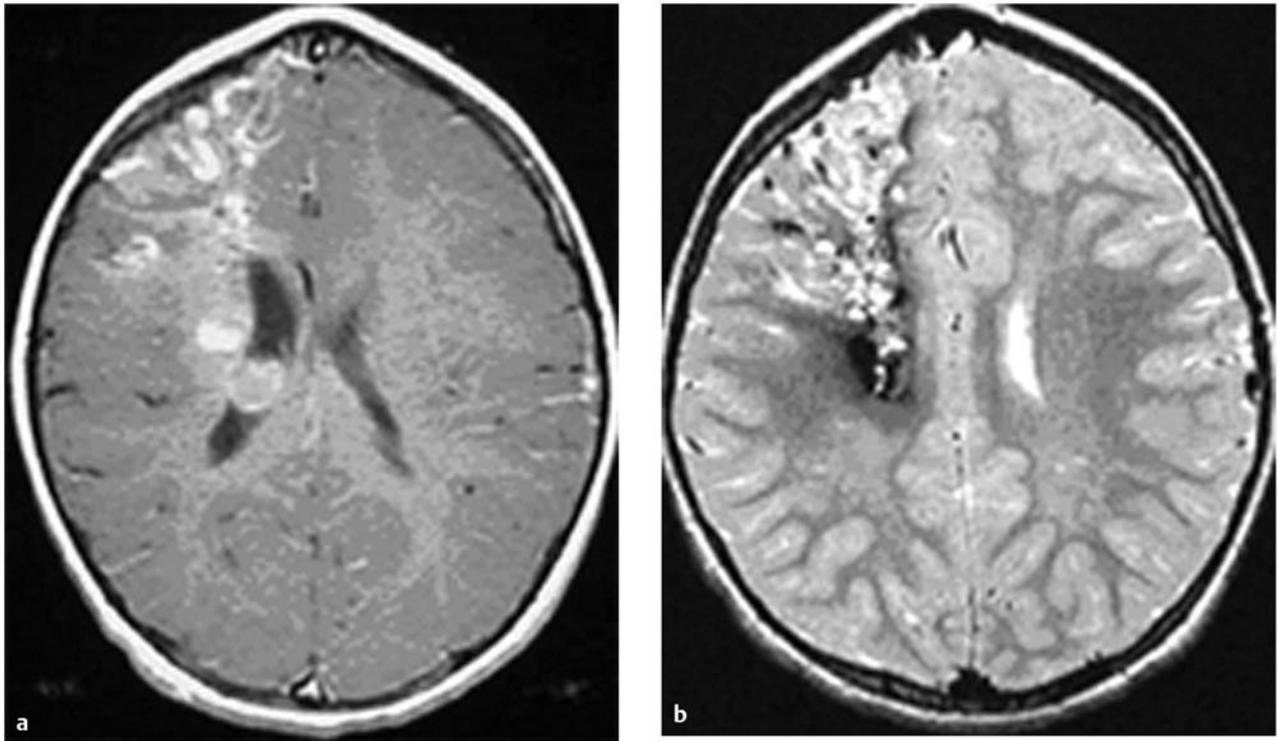


Fig. 64.3 Magnetic resonance imaging studies. (a) T1 with contrast enhancement and (b) T2 demonstrating deep right posterior frontal cavernous malformations with an overlying wedge-shaped cortical venous anomaly and telangiectasia.

► Fig. 64.4, ► Fig. 64.5, ► Fig. 64.6, ► Fig. 64.7, ► Fig. 64.8). On CT, the lesions are often well circumscribed, with hyperdense, bright foci, and blood products or speckled calcification may be present.¹³ MR imaging usually reveals a “popcorn” appearance on T2-weighted images, with evidence of hemosiderin in surrounding tissue.^{17–20} Fluid–fluid levels may be present as well. An important finding is the presence of a DVA, best seen with contrast administration and commonly manifesting the “hydra head” appearance. DVA is found in the majority of pediatric CMs, and the presence of a DVA is important for surgical planning because the prevailing teaching is that this major draining vein should be preserved at resection.^{17–20} CMs are considered angiographically occult, meaning that they are not able to be visualized well (if at all) with catheter-based angiography.²¹

64.5 Differential Diagnosis

In the setting of acute hemorrhage, other lesions, such as arteriovenous malformation (AVM), tumor, and aneurysm, should be considered. If multiple CMs are seen on imaging, the etiology may be familial or related to radiation.²²

64.6 Natural History

The natural history of CMs is difficult to predict. Annual rates of hemorrhage from CMs are about 3% for incidentally found lesions and 4 to 23% for hemorrhagic lesions.^{1,10,23–25} Some hemorrhages can be isolated, whereas others present in clusters. The usual course is an acute headache or deficit, followed by

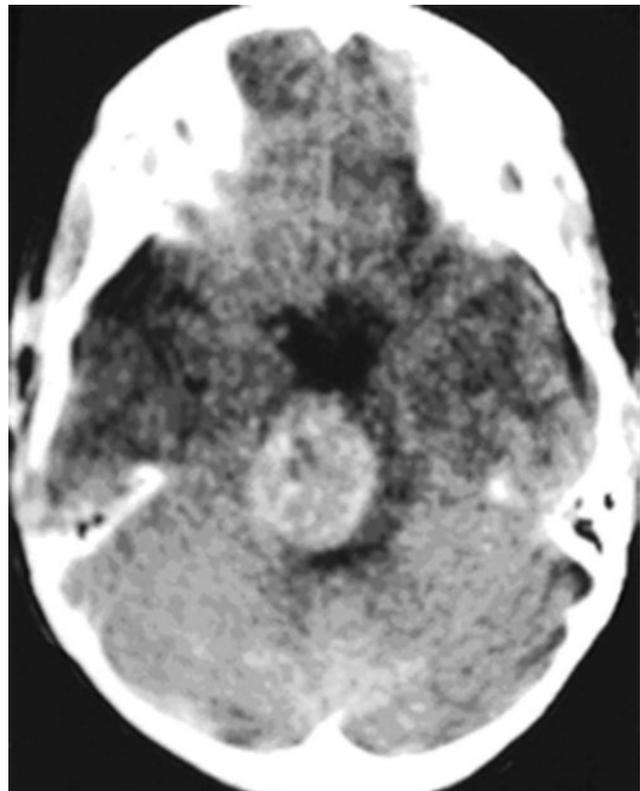


Fig. 64.4 Computed tomographic scan, unenhanced, demonstrating a massive cavernous malformation of the lateral pons and brainstem. The study shows extensive intralésional high-signal attenuation reflecting probable calcium deposition within the lesion.

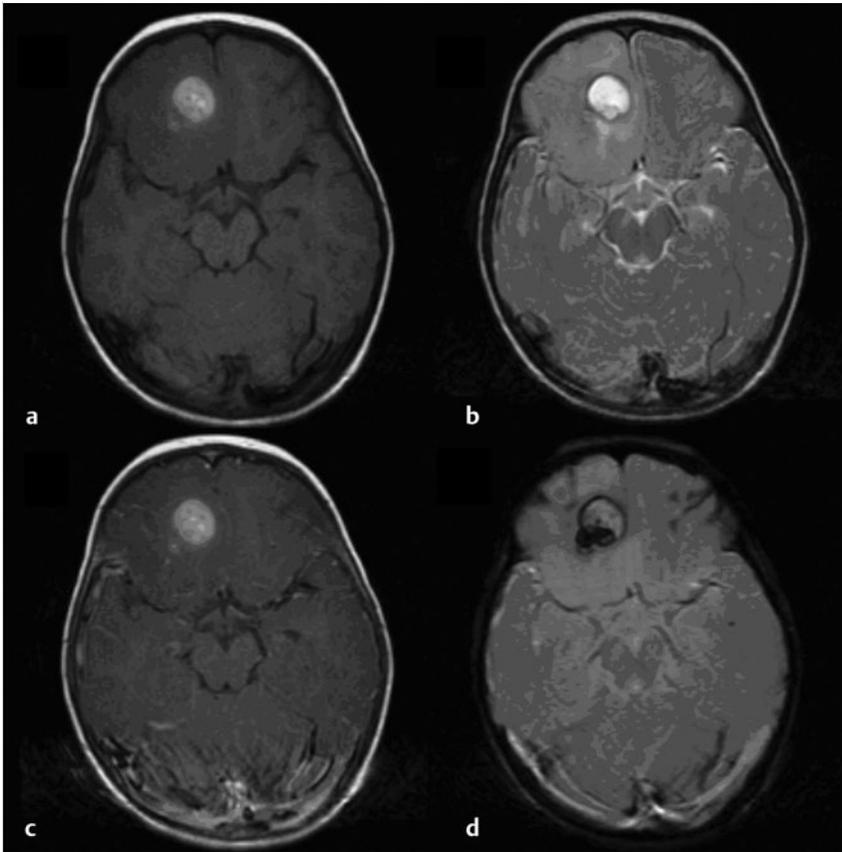


Fig. 64.5 Magnetic resonance imaging sequence. (a) T1, (b) T2, (c) T1 with contrast, and (d) gradient-echo images showing a type 1 lesion in the right frontal lobe.

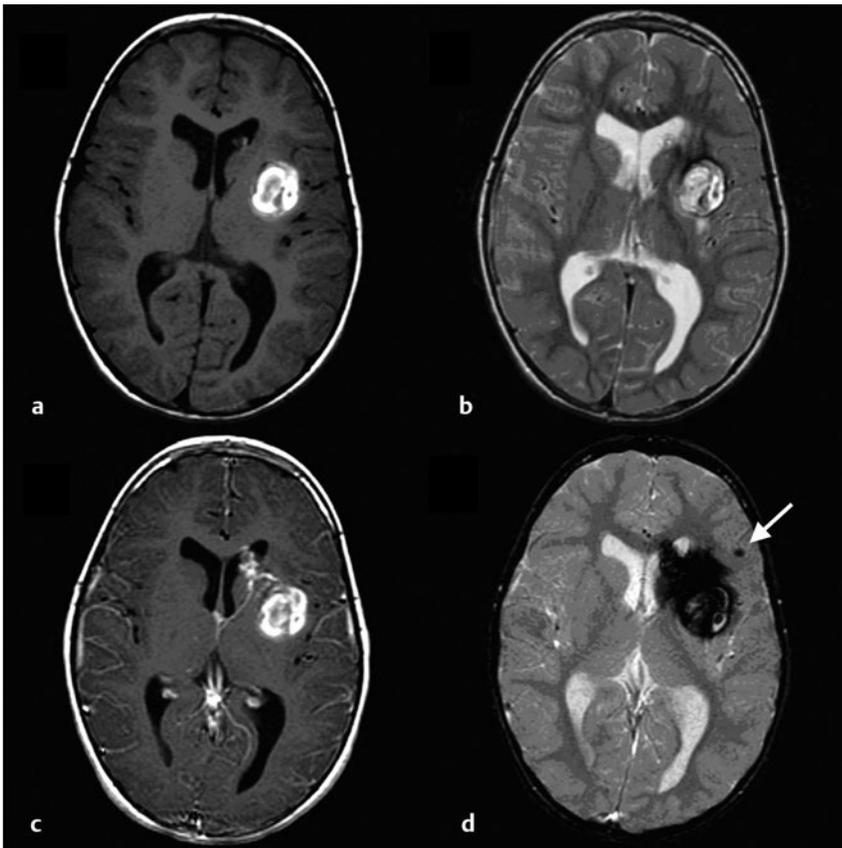


Fig. 64.6 Magnetic resonance imaging sequence. (a) T1, (b) T2, (c) T1 with contrast, and (d) gradient-echo images showing a right-sided type 2 lesion. A small type 4 lesion (arrow) is evident anterolateral to the larger type 2 lesion. In addition, a venous malformation is seen running deep to the cavernous malformation on the contrast scan.

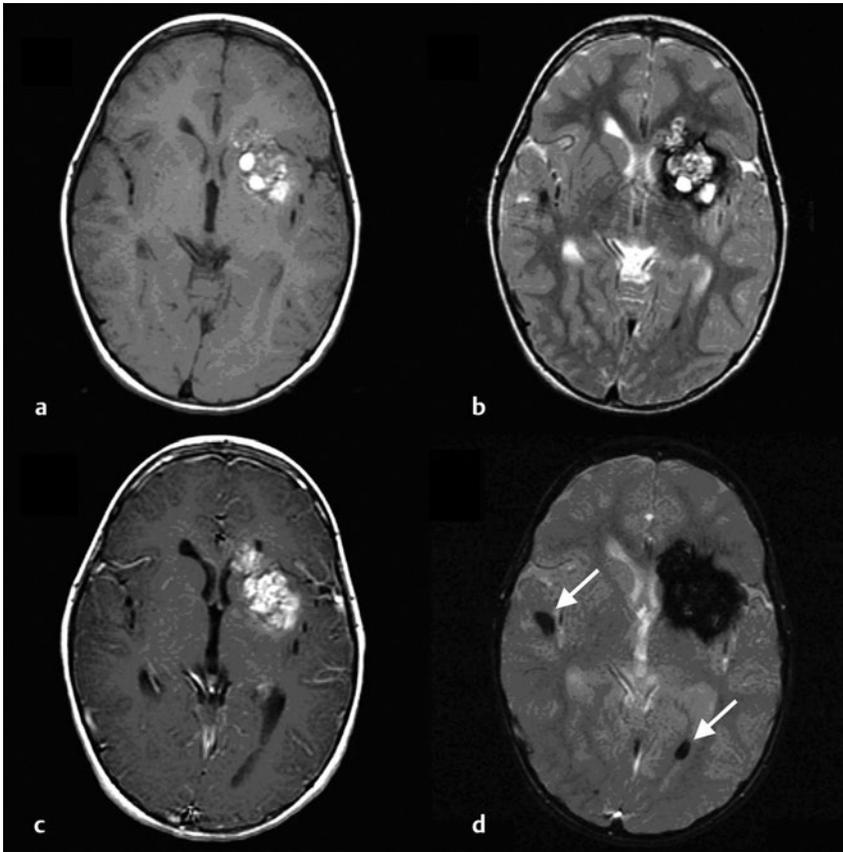


Fig. 64.7 Magnetic resonance imaging sequence. (a) T1, (b) T2, (c) T1 with contrast, and (d) gradient-echo images of the same patient as in ► Fig. 64.6 show a large type 2 lesion, with two small type 4 lesions (arrows) evident on the gradient-echo image.

slow recovery—although often not completely back to baseline—over a few months.^{19,24,26–29}

64.7 Indications for Surgical Treatment

With the natural history as noted, some authors have advocated the early treatment of CMs in children because their anticipated long life span may favor a more aggressive approach.^{12,24,30,31} Symptomatic lesions are resected when feasible. Asymptomatic lesions are more controversial.³² The decision to intervene is especially difficult in the patient who presents with symptoms and has multiple lesions. If the symptoms can be localized to a single lesion that is amenable to surgical resection, then that lesion should generally be removed.^{1,12}

Our practice is to surgically resect a single CM when it is located in non-eloquent cortex, or even in the spinal cord, if the lesion presents with symptoms, documented radiographic enlargement, or hemorrhage (usually after a minimum of about a month following hemorrhage in order to allow swelling to resolve, unless there is urgency because of significant mass effect) (► Fig. 64.9). For a lesion in eloquent cortex or in the brainstem, we commonly observe the lesion initially to determine if it manifests a pattern of recurrent hemorrhage that would justify the risk of surgical intervention. If hemorrhage recurs, then resection is considered. For deep lesions that are surgically inaccessible, we usually observe and treat symptomatically. We do not refer these children for radiosurgery because these malfor-

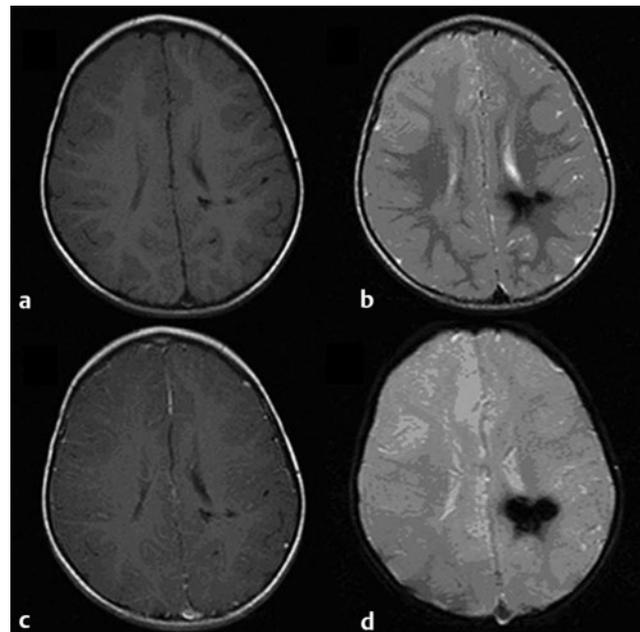


Fig. 64.8 Magnetic resonance imaging sequence. (a) T1, (b) T2, (c) T1 with contrast, and (d) gradient-echo images showing a left-sided type 3 lesion.

mations frequently react to such treatment with brain swelling and prolonged symptoms.

Referrals for genetic counseling are made for children with multiple lesions. If no lesions are symptomatic, we observe

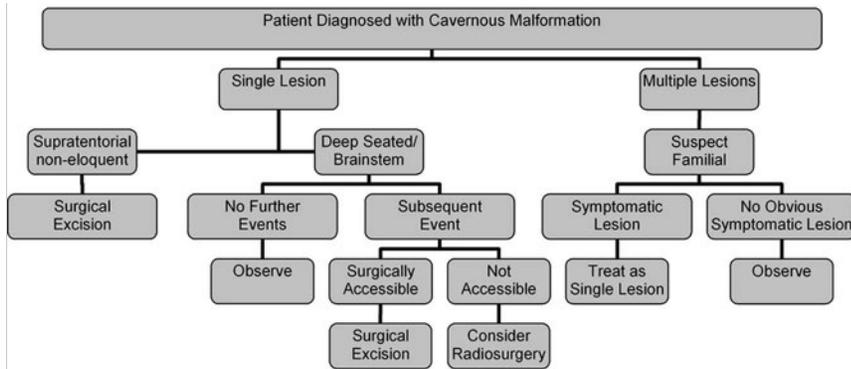


Fig. 64.9 Decision pathway for the management of pediatric cavernous malformations.

them with annual MR imaging studies. If an individual lesion grows, becomes symptomatic, or manifests new hemorrhage on imaging, then we treat following the algorithm detailed in the associated figure.

64.8 Surgical Treatment

The surgical management of CMs in children is similar to that in adults.^{1,9,32,33} In addition to the general principles of removing the entire lesion and preserving normal surrounding vasculature (especially associated DVAs), the resection of a CM may include removal of the surrounding hemosiderin ring if the lesion is cortical, associated with seizures, and in a low-risk location. In practice, the senior author (R.M.S.) rarely pursues excision of the hemosiderin as a separate strategy. In contrast, lesions in eloquent cortex, in the brainstem, or in the spinal cord should generally not have any nonlesional tissue resected in order to minimize injury to sensitive surrounding structures.

At our institution, we have routinely employed frameless stereotaxy to aid in the localization of cranial lesions. This adjunct is particularly useful for deep lesions, and we have found that placement of a catheter along the planned trajectory of approach, after the dura has been opened, is helpful as a guide to the lesion during dissection. We have also found the use of intraoperative ultrasound of immense value for real-time localization and assessment of the extent of resection. The process of resection is aided by the use of nonstick bipolar forceps and the placement of patties to maintain the plane between the lesion and normal brain. We try to avoid entering the lesion, if possible, although in some areas of the brain—particularly the brainstem—this cannot be avoided. The use of gentle coagulation on the surface can often help to reduce the bulk of the lesion while preserving integrity. The use of gentle dissection around the margins of the venous outpouchings with microdissectors will help to tease the malformation out of surrounding brain tissue and help to define dissection planes.

Of critical importance is careful inspection of the surgical cavity—preferably with the operating microscope—at the conclusion of the case. Small fragments of lesional tissue can easily be overlooked, especially if embedded in hemosiderin-stained tissue or when obscured by blood. Removal of the entire lesion will minimize the chance of postoperative recurrence.

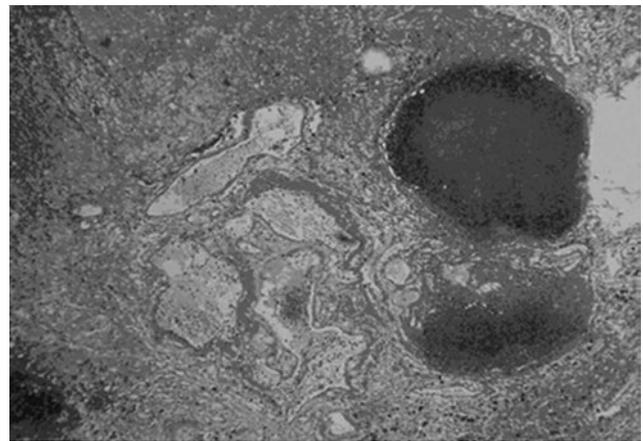


Fig. 64.10 Histologic section of a cavernous malformation that developed following radiation and chemotherapy for the treatment of acute lymphocytic leukemia. The malformation in the left temporal lobe had been treated with stereotactic radiosurgery 6 years previously and continued to bleed and enlarge. The section shows continued patency of many of the vascular channels of the malformation despite the radiosurgical treatment.

64.9 Treatment Alternatives

Radiosurgery has been used for CMs for some time, but its indications remain controversial. It is clear that CMs do not behave in the same way as AVMs that are treated with radiation. Following radiation therapy for CMs, there appears to be a temporary increase in the hemorrhage rate, in some studies up to 22.4% per patient per year³⁴ (► Fig. 64.10). Following a period of 2 to 4 years, the hemorrhage rate decreases, but the results are mixed, with rates from 0.76 to 5% per patient per year. In radiosurgery series, mortality of up to 12% has been reported in brainstem studies.^{34–36}

Morbidity varies among the series, with rates of temporary complications from 10.5 to 59% and of permanent neurologic deficit from 1.7 to 22.7%. It is generally agreed that radiosurgery should not be first-line therapy for CMs and should be reserved for inaccessible lesions that bleed repeatedly. Recent data suggest that more accurate targeting and smaller doses may improve the safety profile for radiosurgery in carefully selected patients with brainstem or surgically inaccessible lesions^{37,38};

however, another alternative is observation, with repeated imaging or clinical examination. For patients with asymptomatic lesions in high-risk surgical locations, it may be reasonable to adopt a practice of watchful waiting, with the understanding that in selected cases, active treatment may potentially carry a greater risk than nonintervention.

64.10 Prognostic Factors

It is difficult to assess the preoperative prognosis of children with CM. Rates of hemorrhage in prospective studies have ranged from 1.6 to 3.1% per patient per year.^{23,24,39} Risk factors for increased hemorrhage rates have also varied between the studies. A higher incidence of hemorrhage at presentation has been found in pediatric series, although some report no rebleeding after subtotal resection in selected cases with up to 10 years of follow-up.^{28,29,40} Some studies have found an increased risk for hemorrhage in patients with previous bleeds, with rates of 3.8 to 23% per patient per year.^{1,40} Hemorrhage rates have been reported to be increased in infratentorial and/or deep lesions in comparison with supratentorial and/or superficial lesions, but this finding may be a consequence of increased, confined neural tract density in these locations.^{24,40,41} Some series, including one in children, showed an increased risk for hemorrhage in female patients.^{10,19,42}

Life-threatening hemorrhage from CMs is less frequent than from AVMs but well documented. In one study, 43.3% of patients had a full recovery following hemorrhage, 23.3% were minimally disabled, 6.7% were moderately or severely disabled, and 20% died.²⁶ In more than 30 years of clinical experience, however, the senior author has never seen a fatality from a CM hemorrhage. Location of the CM is important; deep-seated lesions and brainstem lesions have been shown to have a higher rate of significant events, at 10.6% per patient per year.²⁴ Recovery from these lesions was full in 37% and partial in 36%, with no improvement in the remaining 27%. Children have been found to tolerate supratentorial hemorrhages better than adults.

64.11 Outcomes

Outcomes of surgical therapy have been remarkably good, with most series reporting a nearly 0% mortality rate and a 4 to 5% rate of new permanent deficits.^{27,32} It is important to note that risks greatly increase in sensitive locations, such as the brainstem; rates of new, permanent postoperative deficits range from 12 to 25%, suggesting a need to approach lesions in these areas with caution.^{28,29} CMs can recur if not excised in toto, and a generation of new lesions has been documented, particularly in the setting of radiation-induced lesions and familial cases.^{22,43}

For CMs in high-risk locations, such as the brainstem and eloquent cortex, there is controversy regarding the potential role of radiation as a possible treatment option.^{27,28,44} Radiosurgery has been reported to reduce the frequency of hemorrhage in these lesions from 17.3 to 4.5% per year.^{25,34} However, this decreased rate of hemorrhage comes at the cost of increased complications, including a 16% incidence of new permanent neurologic deficit and a 3% mortality rate.³⁴ As such, the use of

radiosurgery must be balanced against the expected natural history of the lesion. When these data are viewed from the perspective of a child's expectedly long life span and are coupled with the poorly quantified long-term risk for secondary injury from radiation exposure, resection should be considered as first-line therapy whenever possible.

Long-term follow-up with serial MR imaging should be considered. If recurrence is detected, reoperation can be curative. In addition, if seizures remain refractory to medical therapy and can be localized to the resection cavity, referral for a formal epilepsy evaluation may be warranted. In some cases, further operation (sometimes with intraoperative corticography) in order to remove residual hemosiderin can be helpful, with some reports indicating that nearly two-thirds of patients experience significant or complete seizure control after surgery.^{1,2}

64.12 Complications

The risks of surgical intervention vary between series. Mortality is generally low but has been reported to be up to 8% in one series of 100 brainstem CMs, although more than half of the deaths were felt not to be surgically related.^{24,29} Reported overall rates of postoperative morbidity in one large series showed a 20.6% rate of temporary and a 4.1% rate of permanent neurologic deficit.³² Following incomplete resection, repeated hemorrhage and recurrence are reported.

In the current series of CMs at our institution, surgical excision resulted in no mortality. Temporary neurologic worsening occurred in 13% of patients, and 5% had permanent neurologic worsening. Incomplete resection of several CMs did not inevitably result in repeated hemorrhage, and two of our cases with incomplete resection of pontine lesions have had symptom-free postoperative follow-up periods of longer than 20 years.

64.13 Developmental Venous Malformations

DVAs are among the most common cerebral lesions found at autopsy and on imaging. They are usually solitary, except in patients with familial cerebral CMs or extensive craniofacial slow-flow vascular malformations.⁴⁵ The sex incidence rates are approximately equal. These anomalies are usually found incidentally following investigations performed for an unrelated disorder.⁴⁶ The natural history of DVAs is poorly understood. Most seem to follow a benign course, and surgical treatment of these lesions is rarely indicated.⁴⁷ It has been suggested that DVAs in the cerebellar hemispheres are more prone to bleeding than similar lesions in other locations.⁴⁸

DVAs are usually discovered on CT scans. On noncontrast scans, they appear as ill-defined hyperdense lesions without calcification, edema, or mass effect; they often enhance with contrast.¹⁸ CT angiography can also delineate these lesions. MR imaging shows a characteristic abnormality—an enlarged transcerebral draining vein frequently associated with an area of increased parenchymal signal on T2-weighted images and occasionally with reduced parenchymatous signal on T1-weighted images. These lesions enhance with gadolinium and often have a "Medusa head" or "hydra" appearance because of the multiple

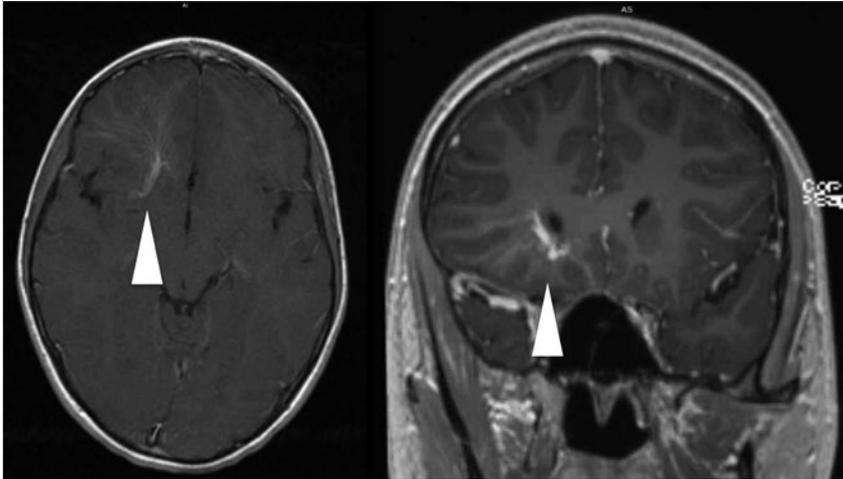


Fig. 64.11 Magnetic resonance images of a typical developmental venous anomaly (DVA), with an axial (left) and coronal (right) T1 postgadolinium sequence. The *arrowhead* in each image notes the classic DVA base with a “Medusa head.”

small veins that center around the large draining vessel¹⁸ (► Fig. 64.11). The characteristic angiographic finding is one of small, radially arranged vessels that converge on a distended vein that, in turn, is connected with the deep venous system or empties into a dural sinus.¹⁸ Frequently, the size of a DVA is inversely proportional to that of the adjacent normal venous channels.⁴⁹ For example, a large DVA in the deep periventricular white matter is typically associated with underdeveloped cortical veins and dilated transmedullary collaterals.

Surgical treatment is not indicated for DVAs. An intracerebral hemorrhage in the presence of a DVA should prompt an investigation for an associated cerebral CM.¹⁸ If a cerebral CM is to be excised, care should be taken to preserve the DVA. Occasionally, a DVA may be associated with other vascular anomalies, and one of our patients has had multiple CMs and a large arteriovenous fistula associated with a large brainstem DVA.

Pearls

- Other diagnostic entities, such as tumor, aneurysm, and AVM, should be carefully considered during the initial evaluation of a patient with CM.
- Surgery should be offered as first-line therapy for symptomatic or growing lesions in accessible regions of the CNS.
- Intraoperatively, care should be taken to maintain the integrity of the lesion if possible while avoiding injury to any associated DVA (if present).
- At the conclusion of the case, meticulous inspection of the surgical cavity—preferably with the operating microscope—is critical to reduce the risk for recurrence from an inadvertently overlooked residual lesion.

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65 Moyamoya Disease

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Moyamoya disease (MMD) is a chronic, idiopathic, steno-occlusive arteriopathy affecting the terminal intracranial internal carotid arteries (ICAs) bilaterally. Often, it also affects the proximal segments of the middle cerebral arteries (MCAs) and anterior cerebral arteries (ACAs), and occasionally the proximal posterior cerebral arteries (PCAs). Multiple small basal collateral vascular channels develop at the skull base and in the basal ganglia. These collateral vessels result in the characteristic appearance on angiography from which the name, moyamoya, which loosely translates to “hazy puff of smoke” in Japanese, is derived.¹ Moyamoya syndrome (MMS) has clinical and angiographic features identical to those of MMD but develops as a result of a known underlying condition, such as Down syndrome, primordial dwarfism, sickle cell disease, or neurofibromatosis. MMS may also develop following radiation treatment.² The mainstay therapy for MMD is surgical revascularization of the affected cerebral hemispheres via direct or indirect techniques.

65.1 Pathophysiology

Although MMD was first described in 1957,³ the underlying etiology of its hallmark stenosis remains unknown. There is no evidence of inflammation or atheroma on histologic examination of pathologic specimens.⁴ MMD vessels demonstrate eccentric fibrocellular thickening of the intima, proliferation of smooth muscle cells in the media, and abnormalities of the internal elastic lamina.⁴ In response to the cerebral hypoperfusion that is secondary to the steno-occlusive disease, there is increased expression of hypoxia inducible factor 1, vascular endothelial growth factor, and basic fibroblast growth factor.⁴ The increased expression of these growth factors is thought to promote the development of the multiple small basal collateral vessels. On histopathologic examination, the vessels are thin-walled, with an incomplete internal elastic lamina and reduced numbers of medial smooth muscle cells. The vessels are therefore at increased risk for the development of aneurysmal dilation and rupture, resulting in hemorrhage.⁴ The staging system of Suzuki and Takaku divides the progression of steno-occlusive disease and collateral development into six sequential stages.¹

65.2 Epidemiology

Pediatric MMD is most prevalent in Japan and Korea, with an estimated prevalence of 9 cases per 100,000 children in Japan.⁵ A recent French study found the incidence of MMD to be 0.065 per 100,000 children per year, with an overall prevalence of 0.39 per 100,000 children.⁵ MMD has a bimodal age distribution; the first peak occurs in the pediatric population (ages 5 to 9 years), and the second in mid adulthood (ages 45 to 49 years).⁶ Although its peak incidence is in children is 5 to 9 years of age, MMD can occur in children of any age, with rare cases reported in infancy.⁷ In children younger than 10 years of age, MMD occurs with equal frequency in boys and girls. In older children, MMD is much more frequent in girls than in boys, with a male-to-female ratio of 2:1.^{6,8} A family history of MMD

is identified in up to 10% of patients.⁹ Unilateral moyamoya occurs in 27 to 39% of patients with MMD or MMS.^{8,10,11}

65.3 Presentation and Natural History

Most commonly, MMD presents in the pediatric population as a transient ischemic attack (TIA) or stroke. These occur from cerebral hypoperfusion secondary to progressive steno-occlusive disease of the ICA, MCA, and/or ACA. Because of the vascular territories affected, TIA or stroke often manifests as hemiparesis, hemisensory loss, dysarthria, or dysphasia. In some cases, the deficits are nonfocal and involve failure to achieve developmental milestones or a deterioration in school performance. In the series of 143 pediatric patients with MMD and MMS reported by Scott et al, stroke had occurred in 68% and TIA in 43% of patients on presentation. Intracranial hemorrhage is an uncommon presentation of patients with pediatric MMD, occurring in 3 to 9% of patients. This is consistent across studies from Asia and North America.^{12,13} Intracranial hemorrhage is thought to be secondary to fragility and/or aneurysmal dilation of the basal moyamoya vessels. Deep intracerebral hemorrhage, intraventricular hemorrhage, or both are the most common patterns of bleeding. Subarachnoid hemorrhage has also been reported. Movement disorder in the absence of stroke or hemorrhage is a rare presentation of MMD. This is thought to be due to dilated moyamoya vessels coursing through the basal ganglia.¹⁴ These patients may present with hemiballismus or chorea. Headache and seizure are other presenting features reported in MMD. MMS found on the screening images of at-risk patients and incidentally discovered MMD are increasingly common as neuroimaging becomes more frequent and awareness of the disease becomes more widespread.

Although the natural history literature for pediatric MMD is somewhat limited, there appears to be nearly uniform progression of the disease, with a high rate of new clinical events in untreated patients. Imaizumi et al followed 15 untreated pediatric patients with MMD until adulthood. Only 4 patients in the series had a good outcome without limitations to activities of daily living, ongoing TIAs, or headaches.¹⁵ In a single-institution series of 35 patients with MMD, 7 of whom were children at the time of diagnosis, Chiu et al reported that the risk for recurrent stroke was 18% in the first year and roughly 5% per year thereafter. Results did not vary with age at presentation.¹⁶

Unilateral MMD has a high rate of progression to bilateral disease. In a series of 18 patients with unilateral MMD followed at Stanford, 39% of patients went on to develop disease in the uninvolved side over a mean of 12.7 months.¹⁰ In a series of 33 patients with unilateral MMD reported by Smith and Scott, progression to bilateral disease occurred in 30% of patients over a mean of 2.2 years.¹¹ The rate of progression to bilateral disease was more rapid in children younger than 7 years at diagnosis, with a mean time to progression of 0.9 year.¹¹

65.4 Clinical and Radiographic Evaluation

MMD should be considered in children who present with symptoms of permanent or reversible cerebral ischemia, especially if the symptoms are triggered by exertion or hyperventilation. All patients should undergo a thorough neurologic assessment, including a history and physical examination. Information regarding neurologic symptoms should be sought, as should evidence of an underlying condition that could suggest MMS. A detailed neurologic examination is essential in order to provide a baseline that can be followed through the perioperative period. A neuropsychological evaluation can help determine if developmental delay or specific functional disabilities are present.

Magnetic resonance (MR) imaging and MR angiography are the first-line investigations in children undergoing a work-up for possible MMD. FLAIR (fluid-attenuated inversion recovery) sequences effectively demonstrate any areas of old infarct, which are often located in the watershed zones between cerebral vascular territories. On FLAIR and contrast-enhanced T1-weighted images, linear cortical hyperintensity (the “ivy sign”) may be seen that is related to slow flow in cortical vessels.^{17,18} Diffusion-weighted imaging is sensitive for acute infarction. On T2-weighted sequences, the normal flow voids of the ICA and MCA are absent or diminished, and multiple small flow voids, representing the moyamoya collateral vessels, may be seen in the basal ganglia and thalamus.¹⁹

Digital subtraction angiography remains the gold standard technique for diagnosing MMD. It demonstrates stenosis or occlusion of the distal ICA with or without involvement of the proximal ACA or MCA. The collateral moyamoya vessels seen at the base of the brain give the “puff of smoke” appearance on angiography. The Suzuki staging system is based on the angiographic findings.¹ For preoperative planning, it is essential that the angiogram include selective external carotid artery (ECA) injections to evaluate the course and caliber of the superficial temporal arteries (STAs).

Perfusion imaging and assessment of the cerebrovascular reserve are an important part of the work-up and surgical decision making for patients with MMD. Multiple modalities are available for assessing cerebral perfusion, including single photon emission computed tomography (SPECT), MR perfusion imaging, BOLD (blood oxygenation level-dependent contrast) MR imaging, CT perfusion imaging, and positron emission tomography (PET). A complete discussion of the attributes of each imaging modality is beyond the scope of this chapter. However, at Stanford, we perform xenon CT or MR perfusion imaging with acetazolamide challenge for the assessment of cerebrovascular reserve in patients with MMD. All patients undergo testing as part of their preoperative work-up and at 6 months postoperatively. Although baseline perfusion imaging is informative, an assessment of the cerebrovascular reserve by means of vasodilator challenge with acetazolamide or hypercapnea provides the best predictor of the territory at risk for stroke. The normal response to vasodilator challenge is an increase in the cerebral blood flow compared with baseline values. In territories with decreased reserve, there is an absence of the normal augmentation of cerebral blood flow or even a steal

phenomenon (reduced cerebral blood flow). This occurs because the vessels are already maximally dilated. In patients with MMD, revascularization surgery is recommended for hemispheres in which an absence of normal augmentation or the steal phenomenon is observed, as either of these portends an increased risk for stroke.

65.5 Indications for Surgical Treatment

Considering the high risk for stroke or recurrent stroke in patients with MMD, surgical revascularization should be offered to all patients with MMD who have symptoms of cerebral ischemia. Surgery should also be offered to asymptomatic patients and patients who present with hemorrhage if there is evidence on perfusion imaging of reduced cerebrovascular reserve, which suggests an increased risk for future ischemic events.²⁰ Patients with unilateral MMD in whom progression on the initially unaffected side is noted on follow-up imaging should also be offered treatment if there is evidence of reduced cerebrovascular reserve on perfusion imaging.²¹

65.6 Surgical Treatment

The surgical treatment for MMD involves revascularization of the affected cerebrovascular territories. This can be accomplished via direct arterial bypass or through indirect revascularization. Direct bypass generally involves anastomosis of an STA to a cortical MCA branch. Other possible donor vessels include the middle meningeal artery (MMA) and the occipital artery, if there is no useable STA. Indirect bypass involves the application of vascularized tissue to the cortical surface of the brain after it has been stripped of arachnoid in order to facilitate the development of collateral blood supply. Commonly used techniques include encephalo-duro-arterial-synangiosis (EDAS) and encephalo-myo-synangiosis (EMS). Other techniques include dural inversion, onlay of pericranium, multiple bur holes, and free or pedicled omental transposition. In the Stanford series of pediatric patients with MMD, 162 hemispheres were revascularized in 96 patients. A direct bypass was performed in 67% of the patients, and an indirect bypass was performed in the remaining 33%. The determining factors precluding direct bypass were size and fragility of the STA or M4 segment in all cases. Indirect procedures were more common in younger children. The youngest child in whom a direct bypass was feasible was 4.3 years old.⁸

We use direct revascularization as often as possible because the immediate benefit of augmentation of blood flow to the affected territory potentially reduces the risk for perioperative infarction. If a direct bypass cannot be performed, generally because of the inadequate caliber of available donor or recipient vessels, we perform an EDAS.

65.7 Perioperative Care and Anesthesia Considerations

The major concern in the surgical management of MMD is the prevention of perioperative strokes. During the immediate

preoperative period, patients should be maintained on antiplatelet therapy, and adequate hydration should be ensured. There is some evidence that hyperventilation (or iatrogenic hypocapnea) may precipitate strokes in patients with MMD. Therefore, it is imperative that painful and fear-provoking stimuli be minimized to avoid triggering inconsolable crying before the induction of anesthesia. During the procedure, iatrogenic hyperventilation must be avoided. This is detected by monitoring end-tidal carbon dioxide or frequently measuring arterial blood gases. Throughout the perioperative and intraoperative period, careful monitoring of the blood pressure is essential, and target pressures should be at or above the patient's baseline blood pressure. After induction, all patients have an arterial line inserted, and most have a central venous catheter placed for intraoperative and postoperative monitoring and management. Intraoperative neuromonitoring, including somatosensory and motor evoked potentials and electroencephalography (EEG), is always used. All changes in potentials are communicated to the anesthesia and surgical team immediately to allow optimization of the cerebral perfusion through maneuvers like elevation of the blood pressure. Mild intraoperative hypothermia, with a goal temperature of 33°C, is employed in all cases. Although there is no rigorous clinical evidence to support the use of hypothermia for focal stroke, theoretical benefits of neuroprotection exist, prospective randomized studies have proved its benefit for global stroke after cardiac arrest and neonatal hypoxic-ischemic encephalopathy,^{22–25} and we have found it to be safe.²⁶ In cases of direct bypass, the mean arterial pressure is raised to 10 mm Hg above baseline, and EEG burst suppression is achieved with the use of propofol during the temporary occlusion of the recipient M4 branch.

65.8 Direct Revascularization with the Superficial Temporal Artery–Middle Cerebral Artery Bypass

For an STA–MCA bypass to be feasible, the donor and recipient vessels must be of sufficient caliber to allow creation of the anastomosis. The minimum caliber of the donor and recipient vessels that we anastomose is 0.6 mm, but vessels should ideally have a diameter of more than 1.0 mm. The donor vessel is chosen preoperatively based on the ECA injection of the angiogram, and the larger STA branch is used. In cases in which the STA branches are similar in caliber, we preferentially use the parietal branch because it is easier to harvest and the incision is more cosmetic. The recipient vessel is chosen intraoperatively based on direct inspection of the exposed M4 vessels.

Following the induction of anesthesia, the patient is positioned supine with a lift under the shoulder and the head turned contralaterally, so that the sagittal plane of the head is parallel to the floor. The Mayfield (Integra, Plainsboro, NJ) three-point fixation system is used in patients undergoing direct bypass to ensure stability of the head during the microanastomosis. The surface projection of the donor STA branch is marked on the scalp with a “pencil” Doppler to identify its course. We prefer to use the parietal branch of the STA. The incision line is marked immediately overlying the STA, with the proximal end anterior to the tragus of the ear. If the frontal branch of the STA is being used,

the incision is kept just behind the hairline, and the distal end is curved posteriorly to allow adequate exposure of the perisylvian region with the craniotomy. Minimal or no hair is clipped for these cases.

The donor vessel is harvested in a proximal-to-distal direction, with the operating microscope used for magnification. The overlying scalp is incised with a scalpel and standard microsurgical techniques. Littler scissors and bipolar cautery are used to isolate the STA. The vessel is isolated circumferentially, with a 4- to 6-mm cuff of fascia on either side of the vessel. Small branches are coagulated and cut, and larger branches are tied off with 4–0 ties. A length of at least 7 cm of STA must be isolated to facilitate performance of the anastomosis. At the proximal end, a short segment of the vessel is denuded of soft tissue to allow temporary clipping and flow measurements. A 1-cm-long segment of the distal vessel is also denuded of soft tissue to facilitate the anastomosis. The STA is left in continuity until immediately before the anastomosis is performed to minimize the risk for vessel thrombosis and also to allow conversion to an EDAS if a suitable recipient vessel is not available (► Fig. 65.1).

Next, the temporalis muscle is incised in a sideways-H fashion, with a cuff of tissue left superiorly to allow reapproximation, and reflected out of the way to expose the underlying skull. A 6×6-cm craniotomy is then performed overlying the sylvian fissure. Meticulous extradural hemostasis is paramount, including dural tack-up sutures, so that run-in blood will not obscure the field when the anastomosis is completed. The dura is then opened in a sideways-H fashion and the dural leaves are reflected.

The exposed cortical surface is examined to identify the largest available M4 branch to act as a recipient vessel. Sometimes, the overlying arachnoid must be stripped to expose the vessels for inspection. Positioning the surgeon perpendicular to the M4 branch makes it easier to sew both walls. Once a suitable recipient is identified, the surrounding arachnoid is opened with standard microsurgical techniques, a segment devoid of branches is identified, and a small piece of high-visibility background is passed beneath the vessel. After a 5-mm temporary aneurysm clip is applied to the proximal donor artery, the distal donor artery is cut at a 45-degree angle (fish-mouthed) to maximize the size of the anastomosis. Any remaining soft tissue is stripped off the distal end. Before the anastomosis is started, the cut-flow through the STA and the M4 branch flow are measured with an ultrasonic flow probe (Charbel Micro-Flowprobe; Transonic Systems, Ithaca, NY).

Before temporary clipping of the M4 branch, EEG burst suppression is achieved with a bolus of propofol, and the patient's blood pressure is raised to 10 to 20 mm Hg above baseline. Temporary aneurysm clips are placed on the proximal and distal M4 branch, with sufficient room left to perform the anastomosis unimpeded. For temporary clipping, specially designed Anspach-Lazic (Peter Lazic GmbH, Tuttlingen, Germany) 3-mm temporary aneurysm clips are used because they have a narrower profile and smaller size than those of standard clips. An elliptical arteriotomy, sized to match the fish-mouthed donor, is made in the recipient vessel with microscissors. Using interrupted 10–0 Monosof (Covidien, Mansfield, MA) suture, the toe and then the heel ends of the anastomosis are sutured in place. The side walls of the anastomosis are then completed. Great care must be taken to avoid catching the back wall of the vessel during suturing. After completion of the anastomosis, the M4

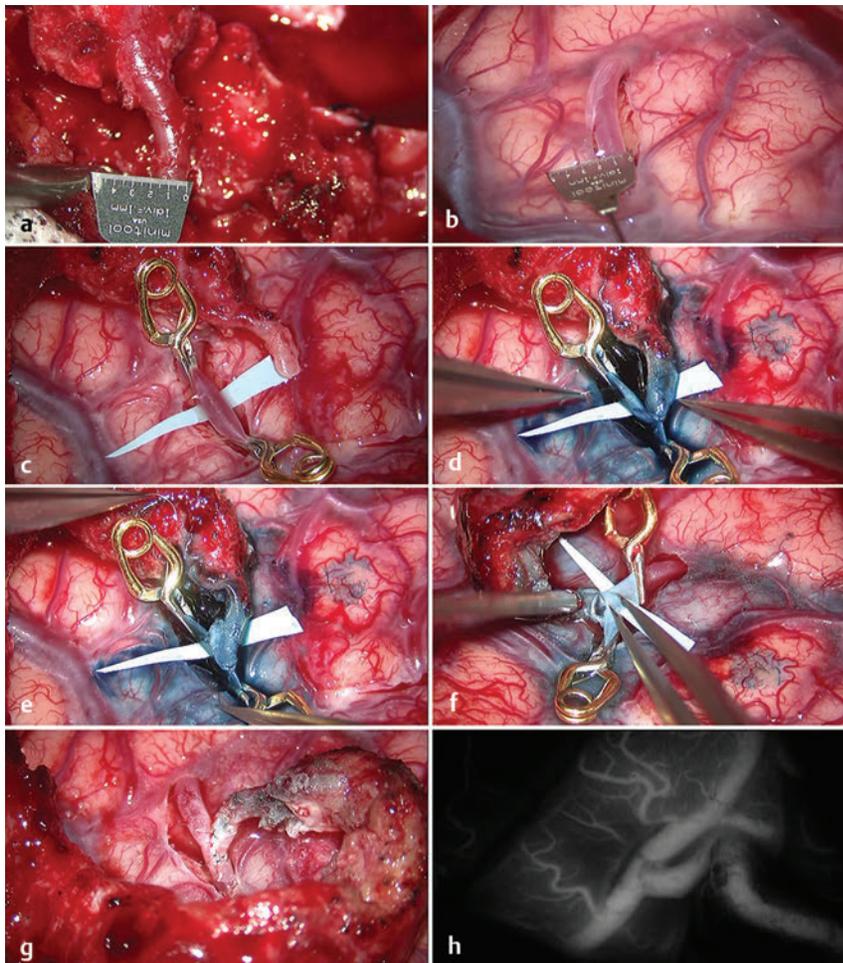


Fig. 65.1 Superficial temporal artery to middle cerebral artery (STA-MCA) bypass for moyamoya disease. (a) The minimum diameter of the distal STA or M4 for completion of an anastomosis is 0.6 mm. Ideally, the vessel diameter should be at least 1 mm. (b) After arachnoid dissection has exposed the M4 branch to be used as the recipient vessel, it is also measured to ensure adequate diameter. (c) Specially designed Anspach-Lazic (Peter Lazic GmbH, Tuttlingen, Germany) 3-mm temporary aneurysm clips are used for temporary occlusion of the recipient M4 branch. These clips have a narrower profile and smaller size than those of standard temporary aneurysm clips, which facilitate completion of the anastomosis. (d) After an elliptical arteriotomy is made in the recipient vessel, the toe of the fish-mouthed STA is sutured in place with 10-0 Monosof (Covidien, Mansfield, MA) sutures. (e) Next, the heel of the STA is sutured. This order allows tailoring of the fish mouth of the STA if there is a mismatch between the donor and recipient vessels. The side walls of the anastomosis are then sutured with interrupted 10-0 Monosof sutures. (f) After completion of the first side wall, the insides of the vessels are checked to ensure that the back wall has not been caught in a suture. (g) The completed anastomosis, with the redundant STA and fascial cuff lying on the cortical surface to allow the further development of indirect collaterals in addition to the direct bypass. (h) Indocyanine green (ICG) video angiography is used to confirm flow through the bypass.

temporary clips are removed and meticulous hemostasis is confirmed. Occasionally, additional sutures must be placed if a leak from the anastomosis occurs. Generally, this is done without repeated temporary clipping. The STA temporary clip is then removed, and hemostasis is confirmed. Flow rates in the proximal and distal M4 and STA are checked with the ultrasonic flow probe (Charbel Micro-Flowprobe), which confirms flow in each limb of the anastomosis. Very high M4 flow rates after bypass have been found to correlate with postoperative hemorrhagic and ischemic complications,²⁷ and in these cases, we control blood pressure more stringently during the postoperative period. Indocyanine green (ICG) video angiography is then performed to confirm bypass patency. The anastomosis is bolstered with small pieces of Surgicel (Ethicon, Somerville, NJ) before closure.

The dura is closed, with a defect left inferiorly to allow the STA to pass through. The bone flap is replaced with titanium plates and screws after a defect has been fashioned in the temporal aspect of the bone to allow passage of the STA without compromise. The temporalis muscle is then reapproximated again, with an opening left inferiorly through which the STA can pass. "Pencil" Doppler is used to confirm that flow in the bypass has not been compromised during closure. The scalp is closed in a layered fashion. In young children, 4-0 Monocryl suture (Ethicon) is used for skin closure. This is done to avoid inflicting pain and inducing crying during suture or staple removal, which may be associated with the induction of TIAs or strokes.

65.9 Other Direct Revascularization Techniques

When the STA is unavailable to serve as the donor vessel, such as in patients who have previously undergone cranial surgery in which the STA was sacrificed, the occipital artery or MMA can be used as the donor vessel. The ECA injection of the preoperative angiogram can be used to determine if either vessel is a potential donor. The segment of occipital artery dissected out must be long enough to rotate to the perisylvian region and bypass to an M4 branch. The MMA can be dissected from between the leaves of the dura and anastomosed to an adjacent M4 arterial branch (► Fig. 65.2).

65.10 Indirect Revascularization with Encephalo-duro-arterial-synangiosis (EDAS)

When direct revascularization is not technically feasible because of the absence or inadequate size of donor or recipient vessels, an indirect revascularization can be performed. At Stanford, we prefer the direct bypass method for its theoretical benefit of immediate revascularization, which may reduce

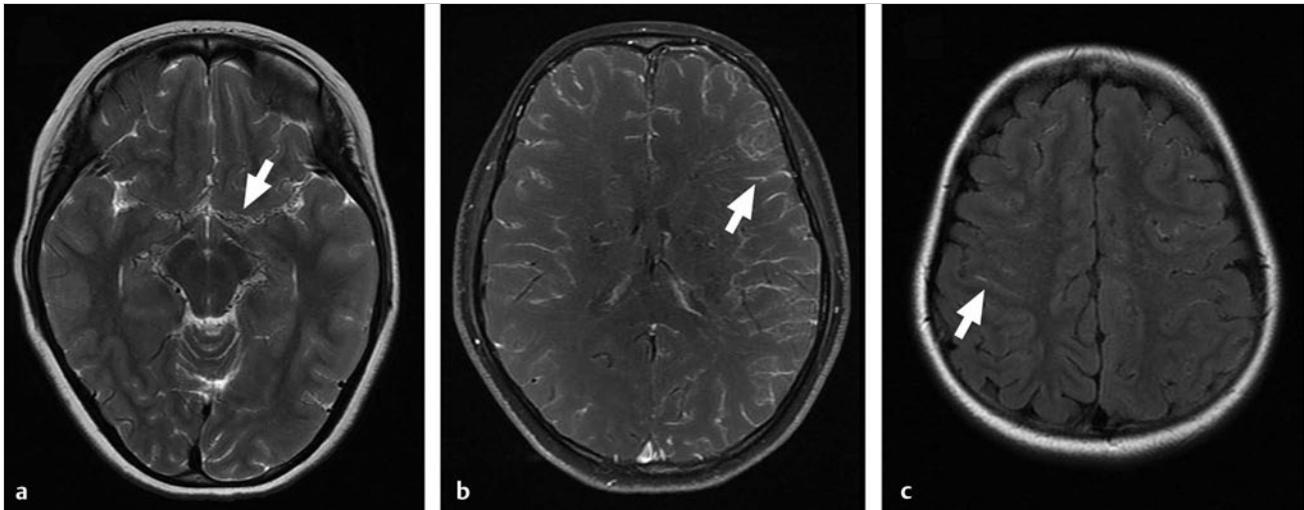


Fig. 65.2 Magnetic resonance imaging of a 10-year-old girl who presented with multiple recurrent transient ischemic attacks causing weakness of the right arm and side of the face. She was neurologically intact at the time of her assessment. T2-weighted image demonstrating multiple small flow voids in the basal cisterns (*arrow*), representing moyamoya collateral vessels (a). T1-weighted gadolinium-enhanced image (b) and FLAIR (fluid-attenuated inversion recovery) image (c) demonstrating linear sulcal hyperdensities (*arrows*), referred to as the “ivy sign,” that are thought to represent slow flow through dilated cortical vessels.

perioperative stroke rates. Other authors favor indirect techniques because they are less technically demanding and can be performed in any patient. Positioning, identification of the STA, and STA harvesting are carried out in a fashion identical to that described above for STA–MCA bypass. When the STA is harvested, a larger fascial cuff is left on either side of the vessel to maximize the surface area for the revascularization. The opening of the temporalis muscle and craniotomy are also performed as described above. It is imperative that the continuity of the STA be preserved throughout the procedure. After the dura has been opened, microsurgical techniques are used to strip arachnoid off the exposed sulci, particularly around cortical vessels. Stripping the arachnoid may facilitate the ingrowth of collateral vessels from the STA.¹³ The STA and its fascial cuff are then placed onto the exposed cortical surface. Some authors advocate using 10–0 pial sutures to secure the fascial cuff to the underlying pia for maximal apposition.¹³ The dura is closed over the STA with a patch of pericranium or Biodesign Surgisis dural graft (Cook Medical, Indianapolis, IN). Defects are left in the dura to allow entry and exit of the proximal and distal ends of the STA, respectively. The craniotomy flap is replaced after sufficient bone has been rongeuired to allow the proximal and distal ends of the STA to pass through without compromise. Closure is identical to that described above for the STA–MCA bypass (► Fig. 65.3).

65.11 Other Indirect Revascularization Techniques

In patients who lack a suitable STA for an STA–MCA bypass or EDAS, other indirect techniques may be employed. EMS with onlay of a portion of the temporalis muscle onto the cortical surface has been shown to effectively revascularize more than one-third of the MCA vascular territory in 75% of patients.²⁸

Because of the size of the temporalis muscle, the territory that can be covered with this technique is somewhat limited. When no other suitable donor tissue is available for revascularization, we have used tunneled or free omental transposition.²⁹ Multiple bur hole surgery has been proposed as a simple technique for providing indirect revascularization. Sainte-Rose and colleagues reported revascularization of 24 hemispheres with this technique (10 to 24 bur holes per hemisphere). They reported excellent revascularization in all treated patients on follow-up angiography.³⁰ At Stanford, when no STA is available for a direct or indirect graft, we have successfully used temporalis muscle or occasionally omental onlay graft. The placement of multiple bur holes or pericranial onlay grafts also sometimes achieves revascularization, although not as consistently as the other techniques.

65.12 Follow-up after Treatment

After revascularization surgery, patients undergo clinical and radiographic evaluation at 6 months, 3 years, 10 years, and 20 years after treatment. At each time point, assessment includes MR imaging, cerebral angiography, and perfusion imaging. To test for adequate revascularization, should the patient continue to have symptoms suggestive of cerebral ischemia, we undertake interim clinical and radiographic evaluation. In patients with unilateral disease, CT angiography is performed annually to check for any development of disease in the unaffected hemisphere (► Fig. 65.4).

65.13 Treatment Alternatives

There are no proven effective nonsurgical therapies for the prevention of stroke in patients with MMD. Endovascular therapy in the form of angioplasty, with or without stenting of the

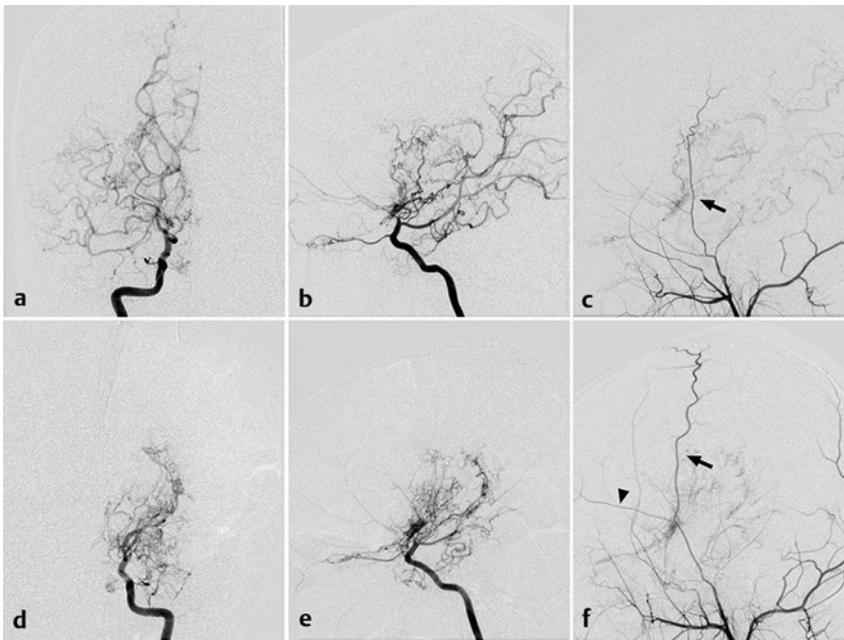


Fig. 65.3 Digital subtraction angiography of the patient described in ► Fig. 65.2. Anteroposterior (a) and lateral (b) projections of a right ICA injection demonstrating occlusion of the ICA distal to the posterior communicating artery and multiple small moyamoya collateral vessels. Lateral projection of the right external carotid artery (ECA) injection (c) demonstrating the parietal branch of the superficial temporal artery (*arrow*). Anteroposterior (d) and lateral (e) projections of a left ICA injection demonstrating occlusion of the ICA distal to the posterior communicating artery and multiple moyamoya collateral vessels. (f) Lateral projection of the left ECA injection demonstrating the frontal (*arrow-head*) and parietal (*arrow*) branches of the superficial temporal artery.

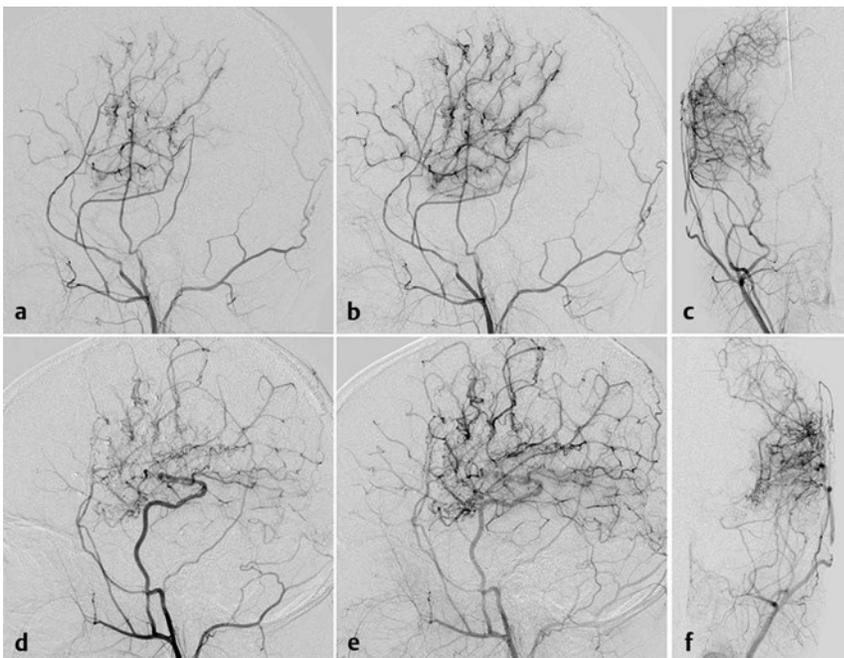


Fig. 65.4 Post-treatment angiogram of the patient described in ► Fig. 65.2 and ► Fig. 65.3. This angiogram was obtained 6 months after bilateral superficial temporal artery–middle cerebral artery (STA–MCA) bypasses for moyamoya disease. The patient had complete resolution of the transient ischemic attacks following surgery and remained neurologically intact. Early (a) and late (b) arterial-phase lateral images and anteroposterior image (c) of a right external carotid artery (ECA) injection demonstrating filling of most of the right MCA territory. Early (d) and late (e) arterial-phase lateral images and anteroposterior image (f) of a left ECA injection demonstrating filling of approximately two-thirds of the left MCA territory.

involved vasculature, has been ineffective. Khan et al reported a series of 5 patients with MMD treated with angioplasty and/or stenting in whom restenosis occurred within 13 months of treatment.³¹ All patients with a diagnosis of MMD are treated with 81 or 325 mg of aspirin daily, which may reduce the risk for thrombus formation or graft stenosis/occlusion. There is no direct evidence supporting the efficacy of this practice, but it is safe. To prevent dehydration from precipitating TIAs or strokes, patients are counseled to maintain adequate hydration at all times and are treated with intravenous fluids throughout any hospitalization.

65.14 Complications

Although cerebral revascularization procedures for MMD are generally safe, there is a risk for stroke or intracerebral hemorrhage in the perioperative period. In the Stanford series of 450 revascularization procedures in adult and pediatric patients with MMD, ischemic stroke occurred in 3% of patients (1.7% of hemispheres) during the perioperative period. Half of these strokes occurred in the treated hemisphere and half in the contralateral hemisphere. By 6 months, half of the patients had made a full neurologic recovery. Transient neurologic episodes

occurred in 3.3% of patients 3 to 7 days after surgery, all of whom recovered fully within 2 weeks. The etiology of these episodes is unclear because there was no MR imaging evidence of stroke; some authors believe they represent cerebral hyperperfusion.³² Intracerebral hemorrhage occurred in 2.6% of patients (1.8% of hemispheres) during the perioperative period. All hemorrhages occurred in previously ischemic territories that had been reperfused, not at the anastomosis sites. Fatal hemorrhage occurred in 0.75% of patients within 30 days of surgery.⁸ In a series reported by Scott et al of 143 pediatric patients with MMD or MMS who were treated with pial synangiosis, the perioperative stroke rate was 7.7% per patient and 4% per treated hemisphere.¹³ Preoperative neurologic instability (major stroke within 1 month before surgery or multiple strokes within 3 months before surgery) was found to be a risk factor for perioperative stroke. This series included 1 acute subdural hematoma and 3 chronic subdural hematomas. There were no perioperative intraparenchymal hemorrhages. In a systematic review of revascularization procedures for pediatric MMD, Fung et al identified 57 articles that documented 1,448 patients. They found the perioperative stroke rate to be 4.4% and the perioperative hemorrhage rate to be 1.7%.³³ Direct revascularization procedures appear to carry a lower risk for perioperative ischemia because of the achievement of immediate revascularization.²¹

65.15 Prognostic Factors

The most powerful predictor of MMD revascularization surgery outcome is the clinical status before treatment. Kim et al found infarction at presentation to be the most powerful predictor of outcome in their series of 410 consecutive cases of revascularization for MMD.³⁴ In the Stanford series of MMD revascularization procedures, Guzman et al also found that children who presented with stroke had an increased risk for surgical complications and that children who underwent indirect revascularization had a 2.5-fold increased risk for perioperative stroke in comparison with their direct-bypass counterparts.⁸

65.16 Outcomes

Outcomes after cerebral revascularization procedures for MMD and MMS are excellent overall. In the series of 410 pediatric MMD cases reported by Kim et al, 81% of patients had resolution of TIAs or seizures after revascularization and achieved a stable or normal neurologic status.³⁴ Perfusion MR imaging and SPECT studies demonstrated improved cerebral hemodynamics in 65% and 60% of patients, respectively. In the Stanford revascularization series, which included adult and pediatric patients with MMD, long-term follow-up showed significant overall improvement in functional status as measured by the modified Rankin Scale score. More than 90% of patients who presented with TIAs were free of TIAs at 1 year or more following surgery.⁸ In their systematic review of pediatric MMD revascularization procedures, Fung et al found that 87% of patients had a reduction or resolution of symptomatic cerebral ischemia at follow-up.³³

On delayed angiography, 99% of bypasses were patent in the Stanford series of bypass for MMD.⁸ Confirmation of

angiographic success is less easily measured after indirect revascularization procedures. In 18 hemispheres (adult and pediatric) treated with EDAS and multiple bur holes, the STA diameters and MMA diameters were both increased by a mean of 50%. A new angiographic blush associated with the STA and MMA was noted in 68% and 78% of hemispheres, respectively.³⁵ On delayed angiography in the series published by Scott et al, 65% of 195 hemispheres that had been revascularized via pial synangiosis demonstrated revascularization of more than two-thirds of the MCA territory. A further 25% showed revascularization of between one-third and two-thirds of the MCA territory.¹³ The long-term efficacy rates of revascularization with direct and indirect techniques in pediatric patients with MMD are comparable, with no other demonstrably superior techniques in the literature to date.²¹

Patients who continue to have TIAs or strokes following revascularization surgery may benefit from repeated revascularization. Pandey and Steinberg reported complete resolution of TIAs and no new strokes in 80% of patients who underwent repeated revascularization in a series of 16 patients (10 pediatric patients). One patient died, and no other patients worsened neurologically after repeated surgery.³⁶

65.17 Conclusion

MMD is a treatable cause of pediatric ischemic stroke. Surgical revascularization is the only effective treatment for preventing stroke in this patient population. Symptomatic patients and patients with imaging evidence of decreased cerebrovascular reserve should be offered surgical revascularization. Outcomes following revascularization are excellent, with low rates of new or recurrent stroke or TIA.

Pearls

- Revascularization surgery should be offered to all patients with MMD who have symptomatic cerebral ischemia or imaging evidence of reduced cerebrovascular reserve.
- Direct STA–MCA bypass provides immediate revascularization and thus appears to have a slightly lower risk for perioperative stroke than indirect revascularization.
- Direct STA–MCA bypass is not technically feasible in all children with MMD. Inadequate size of STA or recipient M4 branches is the most common reason why direct bypass cannot be performed.
- Indirect revascularization techniques also provide safe, effective revascularization of cerebral territory at risk for stroke in patients with MMD.

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66 Intracerebral Aneurysms

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Pediatric intracerebral aneurysms are rare, having an overall incidence of 0.6%,¹ and are even rarer in infancy.² The annual incidence of new intracerebral aneurysms in children has not been reported. The annual incidence of hemorrhagic stroke from newly diagnosed intracerebral aneurysms in children is 0.18 per 100,000. Approximately 800 cases of pediatric intracerebral aneurysms have been reported in the literature to date, mostly in the form of case reports and series. However, because of the threat of rupture with potentially devastating neurologic sequelae, it is imperative that pediatric specialists make the appropriate diagnosis and initiate multidisciplinary treatment in a timely manner. Pediatric patients' extremely long life expectancy following treatment likewise demands that treatment durability be critically assessed.

The mantra in pediatric specialties is that "children are not little adults." The management of pediatric intracerebral aneurysms embodies this concept. Pediatric aneurysms differ from those in the adult population with respect to aneurysm presentation, location, size, morphology, and natural history. In fact, it has been proposed that pediatric and adult aneurysms are distinct pathologic entities. Whereas aneurysms in adults are more prevalent in women, those in children show a slight male predominance.³ Some have noted a bimodal age distribution in the pediatric age group. In modern series, subarachnoid hemorrhage is not the most common presentation.^{4,5} Saccular aneurysms are more likely to present with subarachnoid hemorrhage, whereas fusiform aneurysms are more likely to present with symptoms of mass effect.⁴ When subarachnoid hemorrhage is present, it generally manifests with a low grade on the Hunt and Hess Scale.^{6,7} The incidence of clinically significant vasospasm after rupture is also significantly lower.^{8,9} Nevertheless, cerebral infarction secondary to vasospasm does occur in children and should be recognized and treated expeditiously.^{7,10,11}

Aneurysms are most often located at the internal carotid bifurcation.^{7,8,12,13} Compared with those in adults, pediatric aneurysms are more commonly located in the posterior circulation and are more likely to be giant.^{3,5,6} Fusiform morphology is relatively more common in children.^{5,14} Infectious ("mycotic") aneurysms are generally located either distally in cortical vessels or close to the skull base and cavernous sinus, are usually fusiform, and may be multiple. Pediatric aneurysms demonstrate the capacity to arise *de novo* and to grow rapidly.^{3,15,16}

66.1 Diagnosis and Initial Management

The initial test in a child with suspected subarachnoid hemorrhage is noncontrast computed tomography of the head. Subarachnoid hemorrhage is the most common pattern of bleeding observed in children with ruptured intracerebral aneurysms. Intracerebral hematoma with or without subarachnoid hemorrhage is rare. In patients with a convincing history to suggest subarachnoid hemorrhage but without CT evidence of blood products, a lumbar puncture should be performed. Blood in the cerebrospinal fluid (CSF) or on a CT scan is further evaluated by

vascular imaging. Despite significant advances in CT angiography and magnetic resonance (MR) angiography, conventional four-vessel angiography remains the gold standard for defining the intracranial vascular anatomy. For patients with unruptured aneurysms, MR angiography may be the initial imaging modality. The choice of imaging modality is individualized on a case-by-case basis, with the goal of reducing radiation exposure while obtaining the necessary information to plan subsequent interventions.

Patients who present with a Glasgow Coma Scale score of 8 or less require intracranial pressure monitoring. External ventricular drains are preferred over intraparenchymal pressure monitors because they offer the possibility of CSF drainage to treat elevated intracranial pressure and hydrocephalus and the drainage of blood products in patients with intraventricular hemorrhage. External ventricular drainage is continued peri- and postoperatively. In general, the use of ventricular catheters is continued for the duration of the vasospasm risk period (days 3 through 17 after the bleed). There are cases of children who have reliably improving neurologic examinations with no imaging evidence of ventriculomegaly and a low Fisher grade in whom early removal of the external ventricular drain can be considered. Patients with significant intraventricular blood require ventricular drainage until the CSF is clear of blood products. Before removal of the external ventricular drain, the drain is clamped and the neurologic examination is followed closely. If the examination remains stable, a CT scan of the head is obtained after 24 hours of clamping. If the ventricular size is stable, the ventricular drain is removed. Children who fail this "clamp trial" require ventriculoperitoneal shunting.

66.2 Indications for Surgical Treatment

66.2.1 Subarachnoid Hemorrhage

In a large historical series from 1971, Patel and Richardson reported on 58 pediatric patients who presented with ruptured aneurysms, 21 of which were treated medically.⁹ Of these patients, 12 died and only 8 survived without neurologic deficits. Storrs et al demonstrated that children with previously untreated subarachnoid hemorrhage had a worse grade when they presented for treatment and subsequently had worse outcomes.¹² This was also noted by Sharma et al.⁷ Therefore, presentation with subarachnoid hemorrhage from a ruptured aneurysm is an absolute indication for treatment. Symptoms of subarachnoid hemorrhage range from the acute onset of a severe "thunderclap" headache, meningeal signs (photophobia, nuchal rigidity), and seizure to a comatose state. Children tend to have a greater capacity than adults to recover after rupture, and we generally maintain an aggressive treatment posture for pediatric patients with aneurysms, even those presenting with poor grades on the Hunt and Hess Scale (► Fig. 66.1a–d).

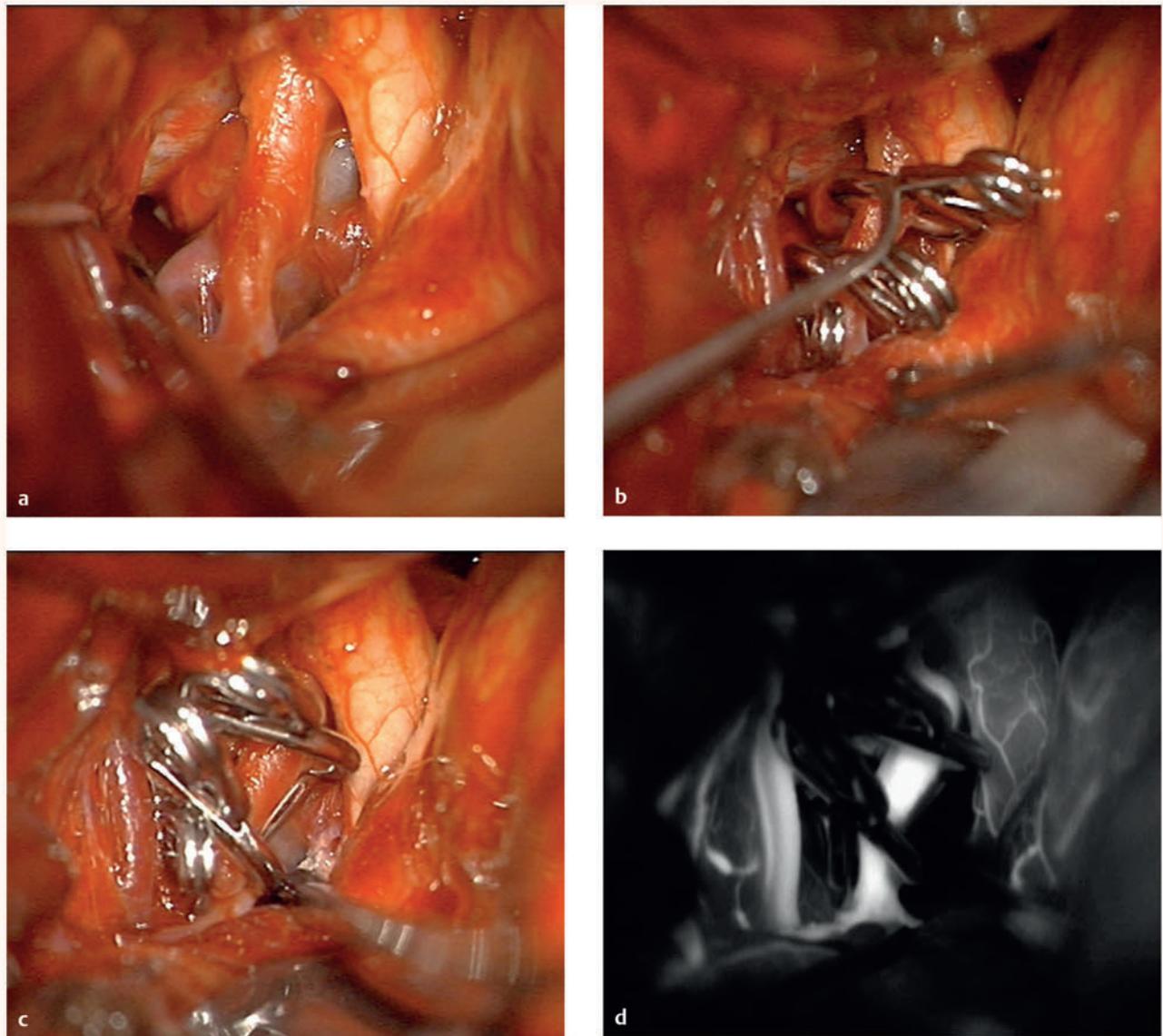


Fig. 66.1 (a) This 5-year-old girl presented with subarachnoid hemorrhage from a giant, thrombotic left internal carotid artery (ICA) aneurysm that was multilobulated. (b) Left pterional craniotomy exposed the aneurysm, which was clipped with two tandem right-angled fenestrated clips around the ICA. (c) A third clip occluded the posterior communicating artery as it exited the aneurysm. (d) Intraoperative indocyanine green dye demonstrated patency of the ICA and its branches.

66.2.2 Mass Effect

Pediatric patients who have an aneurysm with fusiform morphology, more than one aneurysm at presentation, and superimposed medical comorbidities are at increased risk for aneurysm enlargement or the development of new aneurysms.¹⁵ Symptoms attributable to mass effect range from headache, dizziness, and cranial nerve palsies to mono- or hemiparesis. Presentation with an enlarging aneurysm and progressive symptoms is an absolute indication for treatment.

66.2.3 Trauma

Traumatic aneurysms are associated with closed head injuries or penetrating head trauma. They are commonly associated

with skull base fractures. The injury induces a longitudinal vessel tear with the creation of a false lumen and subsequent dissection. Some are pseudoaneurysms, with injury to all vessel wall layers and hematoma encapsulation, having the imaging appearance of a true aneurysm. The supraclinoid internal carotid artery is the most common location for traumatic aneurysms. This anatomical location is most vulnerable because the proximal internal carotid artery is fixed at the dural entry by the distal dural ring and is more mobile distally where the carotid artery bifurcates to form the anterior cerebral and middle cerebral arteries. Particularly in a patient with a history of head trauma, a noncontrast CT scan demonstrating subarachnoid hemorrhage may be misinterpreted as traumatic subarachnoid hemorrhage. Because trauma can be associated with true or false aneurysms, subsequent vascular imaging is necessary. It

has been proposed that traumatic aneurysms may have a more favorable natural history because the artery involved is inherently normal and has the capacity to heal, whereas saccular or fusiform aneurysms arise from abnormal vessels.⁴ Nonetheless, traumatic dissecting aneurysms that present with subarachnoid hemorrhage are at risk for repeated hemorrhage, and treatment must be considered.

66.2.4 Infection

Infectious or mycotic aneurysms arise in the setting of endocarditis, septicemia, or human immunodeficiency virus infection.

Unruptured infectious aneurysms can be treated with appropriate intravenous antibiotics and frequent surveillance catheter angiography to document resolution or stabilization. However, documented growth or rupture of the aneurysm is an indication for definitive treatment (► Fig. 66.2a–k).

66.3 Surgical Treatment

Because of the complex and variable morphology of pediatric intracerebral aneurysms, a wide range of microsurgical techniques are required for their treatment. In an institutional series,

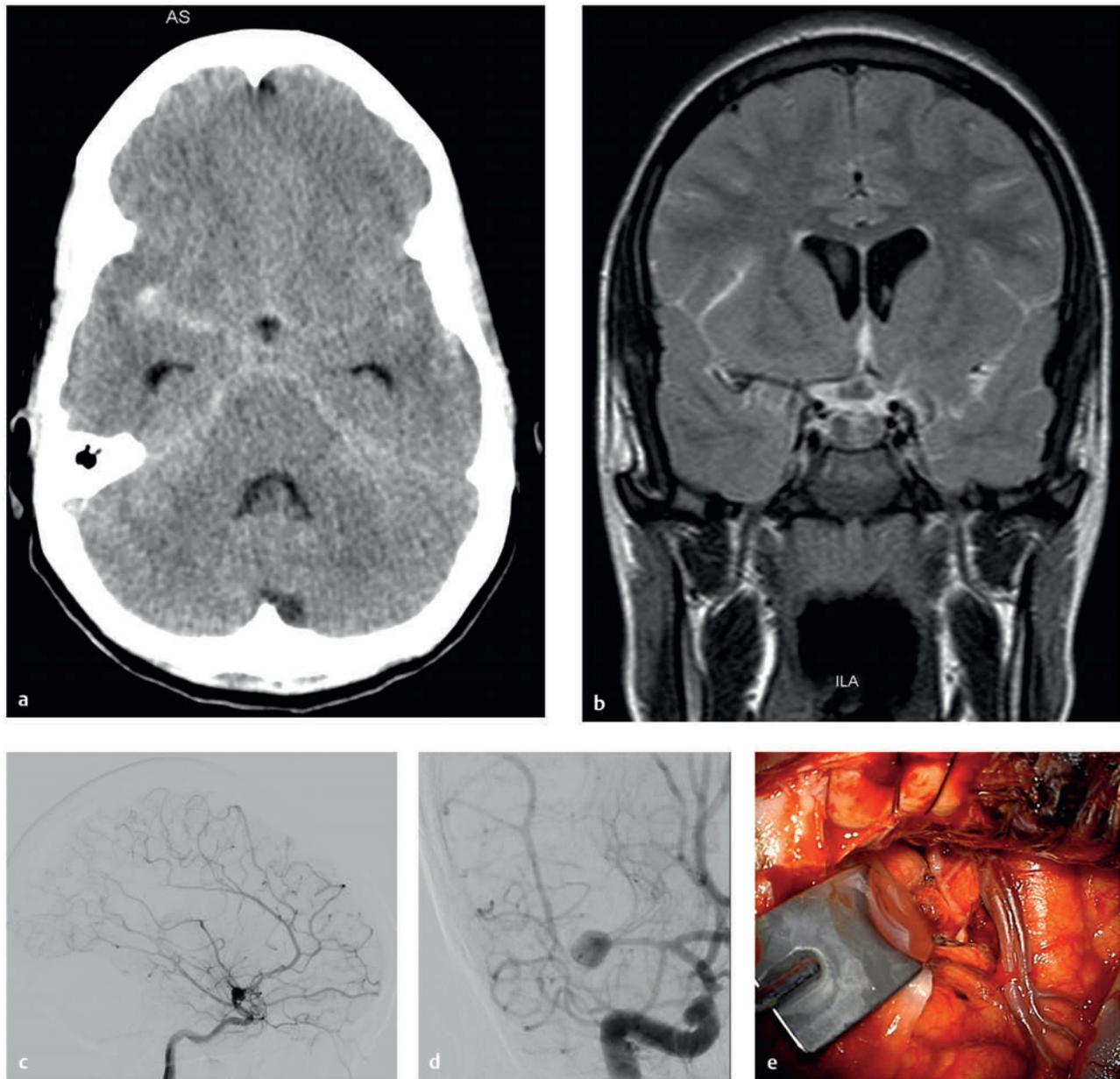


Fig. 66.2 This 17-year-old girl had a history of congenital heart disease and valve replacement surgery. (a) She presented with a subarachnoid hemorrhage as seen on an axial computed tomographic scan, and (b) a mycotic middle cerebral artery (MCA) aneurysm was seen on a magnetic resonance image. The aneurysm enlarged rapidly despite antibiotics, (c,d) as seen on catheter angiography, and she was transferred for surgical care. Note that the superior MCA trunk was occluded at this time. (e) The aneurysm was exposed through a right orbital-pterional craniotomy, (*continued*)

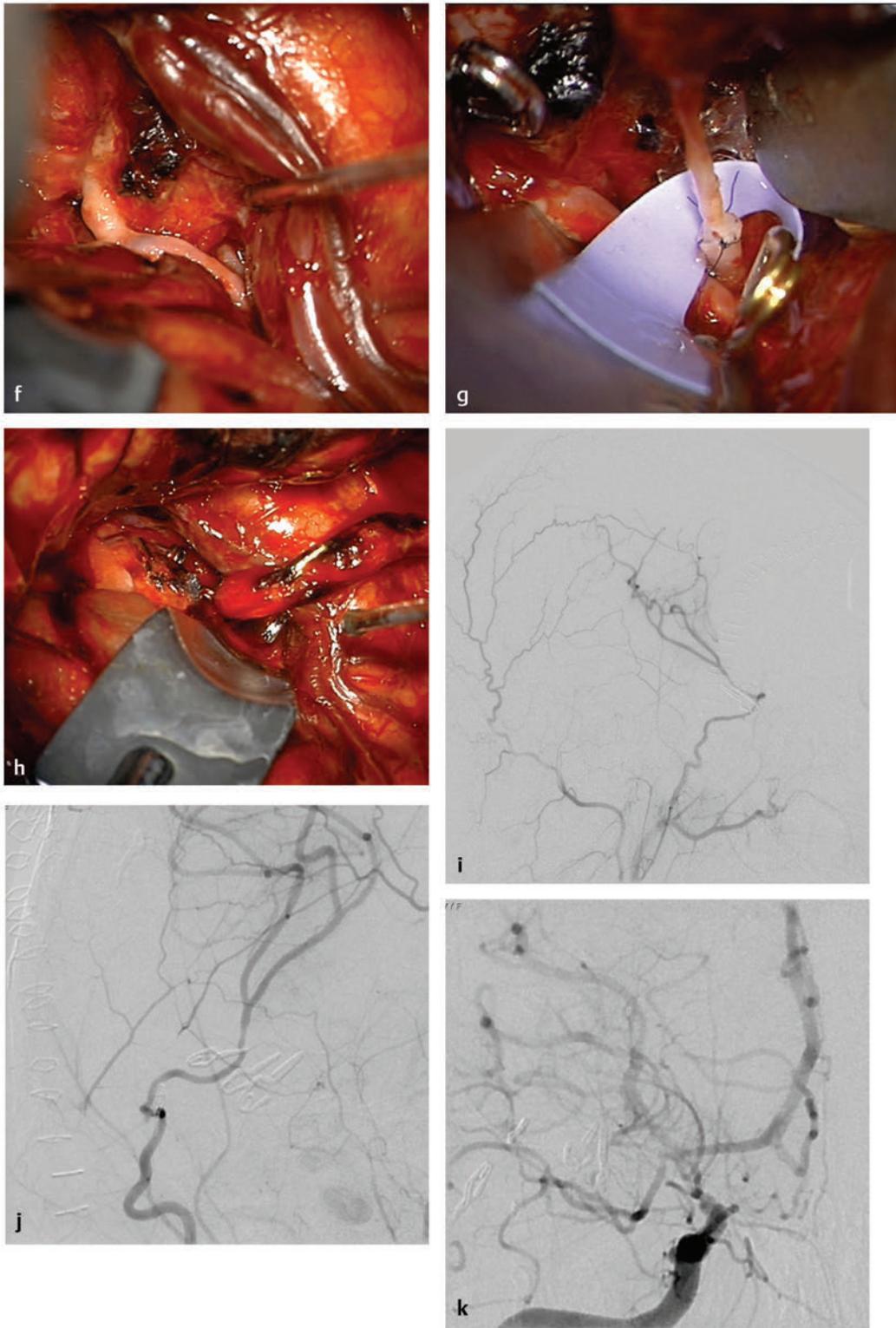


Fig. 66.2 (continued) and (f) inspection confirmed a mycotic aneurysm and a superior trunk occlusion. (g) The inferior trunk was revascularized with an end-to-end superficial temporal artery-to-MCA bypass, and (h) the aneurysm was trapped. (i,j) Post-operative angiography demonstrated the bypass filling the inferior trunk and angular arteries, and (k) the aneurysm was excluded completely with preservation of the lenticulostriate arteries.

we reported 13 patients treated initially with microsurgical techniques.⁵ Treatment techniques included direct surgical clipping, aneurysm trapping alone, trapping with extracranial-to-intracranial bypass, aneurysm excision with anastomosis, and proximal artery occlusion. A small number of patients in the initial microsurgical group required subsequent surgical or

endovascular treatment, underscoring the importance of interdisciplinary treatment planning and vigilant follow-up.

The variety of locations of pediatric intracerebral aneurysms mandates that the vascular neurosurgeon be comfortable with the different approaches to these anatomical locations. The standard pterional craniotomy gives access to many of the

anterior circulation aneurysms. The pterion, the lesser wing of the sphenoid, and the squamous portion of the temporal bone are removed with a high-speed drill in order to create a smooth, flat surface over the orbit connecting the anterior and middle cranial fossae. This allows an unobstructed view into the carotid cistern once the dura is opened and reflected. The orbitozygomatic craniotomy allows access to basilar tip aneurysms and can be used to gain greater exposure to giant and complex anterior circulation aneurysms. This approach includes the pterional craniotomy supplemented with removal of the orbital rim, orbital roof, lateral orbital wall, and zygomatic arch. Bifrontal craniotomy is used to approach pericallosal artery aneurysms. The medial border of the bone flap crosses the superior sagittal sinus, allowing exposure of the interhemispheric fissure once the dura is reflected medially. Care must be taken with bridging veins during this approach. Posterior inferior cerebellar artery aneurysms and aneurysms of the vertebral artery are approached through a far lateral craniotomy. This involves a C1 laminotomy, lateral occipital craniotomy, and condylectomy.

The treatment of choice for nongiant saccular aneurysms is direct surgical clipping. An aneurysm with a narrow neck and an uncomplicated anatomy can be clipped with a single appropriately sized and contoured clip. For an aneurysm with a broad neck or more complex anatomy, multiple clips oriented in intersecting, stacked, or overlapping configurations may be required. Giant saccular and fusiform aneurysms can also be treated by surgical clip reconstruction. In this technique, the arterial lumen is reconstructed with multiple surgical clips when a large size, wide neck, and/or abnormal branches prevent simpler clip applications. Complex clip reconstruction often requires proximal and distal temporary clips to soften the aneurysm, and it may be necessary to open the aneurysm to deflate it or remove thrombus intraluminally. Aneurysms not amenable to direct clipping may need to be trapped and bypassed ▶ Fig. 66.3a–m). A small subset of aneurysms can be excised with end-to-end anastomosis of the normal artery ends; however, this requires enough slack on either end for the ends to be brought together and sutured without tension.

Infectious aneurysms typically contain an infected arterial wall that must be completely excluded from the circulation. Therefore, aneurysm trapping is the preferred treatment, with bypass if needed. Traumatic aneurysms also have a weakened arterial wall that may not be able to hold a surgical clip, or the arterial wall may be involved circumferentially, in which case trapping and bypass is the preferred option.

Because of the large size and complex anatomy of some pediatric intracerebral aneurysms, surgical adjuncts such as cardiac standstill can be considered.^{11,17} Particularly useful for giant vertebrobasilar aneurysms, deep hypothermic circulatory arrest allows the giant aneurysm to be collapsed without bleeding, and dissection of the aneurysm can be performed without risk for rupture.¹⁸ However, this extreme intervention is becoming increasingly rare because bypass options, endovascular options, and combined therapies offer lower-risk alternatives.

Although not a definitive treatment and considered a treatment of last resort, aneurysm wrapping with muslin or other reinforcing material is also an option when other options fail.^{11,17}

66.4 Outcomes

Microsurgery is very successful at treating pediatric aneurysms definitively. In our series of aneurysms treated microsurgically, we reported a 93% rate of complete aneurysm obliteration.⁵ There were no recurrences at long-term follow-up. An 8% rate of formation of de novo aneurysms was noted. Others have reported similarly good results, with durable aneurysm cure after surgical therapy. Repeated hemorrhage is rare after treatment. In the Barrow Neurological Institute series of 48 children, reported by Kakarla et al, there was 1 event of repeated hemorrhage, which led to the only mortality.¹⁷ Lasjaunias et al reported 5 cases of repeated hemorrhage in a series of 59 children.¹⁴ There were 3 cases of repeated hemorrhage in 33 children with fusiform aneurysms, leading to 2 deaths and 1 poor neurologic outcome. In addition, there were 2 cases of repeated hemorrhage in 8 infectious aneurysms, both of which resulted in death.

In our series, 78% of patients treated microsurgically had good outcomes, defined as a Glasgow Outcome Scale scores of 4 or 5, indicating moderate disability or better. In a series of 13 pediatric intracerebral aneurysms treated with microsurgery, including 9 that were ruptured, Huang et al reported good outcomes in 95%.¹⁹ Similarly, in a large single-surgeon series of 52 patients with long-term follow-up, Aryan et al reported good to excellent neurologic outcomes in 81% of patients treated surgically.¹¹

In all large series of pediatric intracerebral aneurysms, aneurysm wrapping is a rare treatment modality. It appears that aneurysm size in patients who undergo wrapping remains stable; however, this is based on very low numbers reported.

66.5 Complications

66.5.1 Intraoperative Complications

Intraoperative aneurysm rupture is a reality of aneurysm surgery, regardless of the surgeon's skill and experience. Aryan et al reported 6 intraoperative aneurysm ruptures in their series of 52 operations (12%), which included 35 subarachnoid hemorrhages.¹¹ Kakarla et al reported a slightly lower rate of intraoperative ruptures: 2 in 54 operations (4%), including 16 subarachnoid hemorrhages.¹⁷ The immediate response to intraoperative rupture must be direct pressure with cottonoid, suction, temporary clipping, or trapping, followed by permanent clipping. Potential points of proximal control are identified preoperatively on angiography and are prepared early in the dissection. These may include the neck, which is prepared to gain access to the cervical internal carotid artery for proximal control of an ophthalmic artery aneurysm. Other points of control include the ophthalmic segment of the internal carotid artery for posterior communicating artery aneurysms, the M1 segment for middle cerebral artery aneurysms, bilateral A1 segments for anterior communicating artery aneurysms, the A2 segment for pericallosal artery aneurysms, the basilar trunk for basilar tip aneurysms, and the intradural vertebral artery for posterior inferior cerebellar artery aneurysms.

Perforating artery injury can be devastating. Liang et al reported 1 perforator injury in 4 pediatric aneurysms treated microsurgically.⁶ This perforator injury resulted in the only death

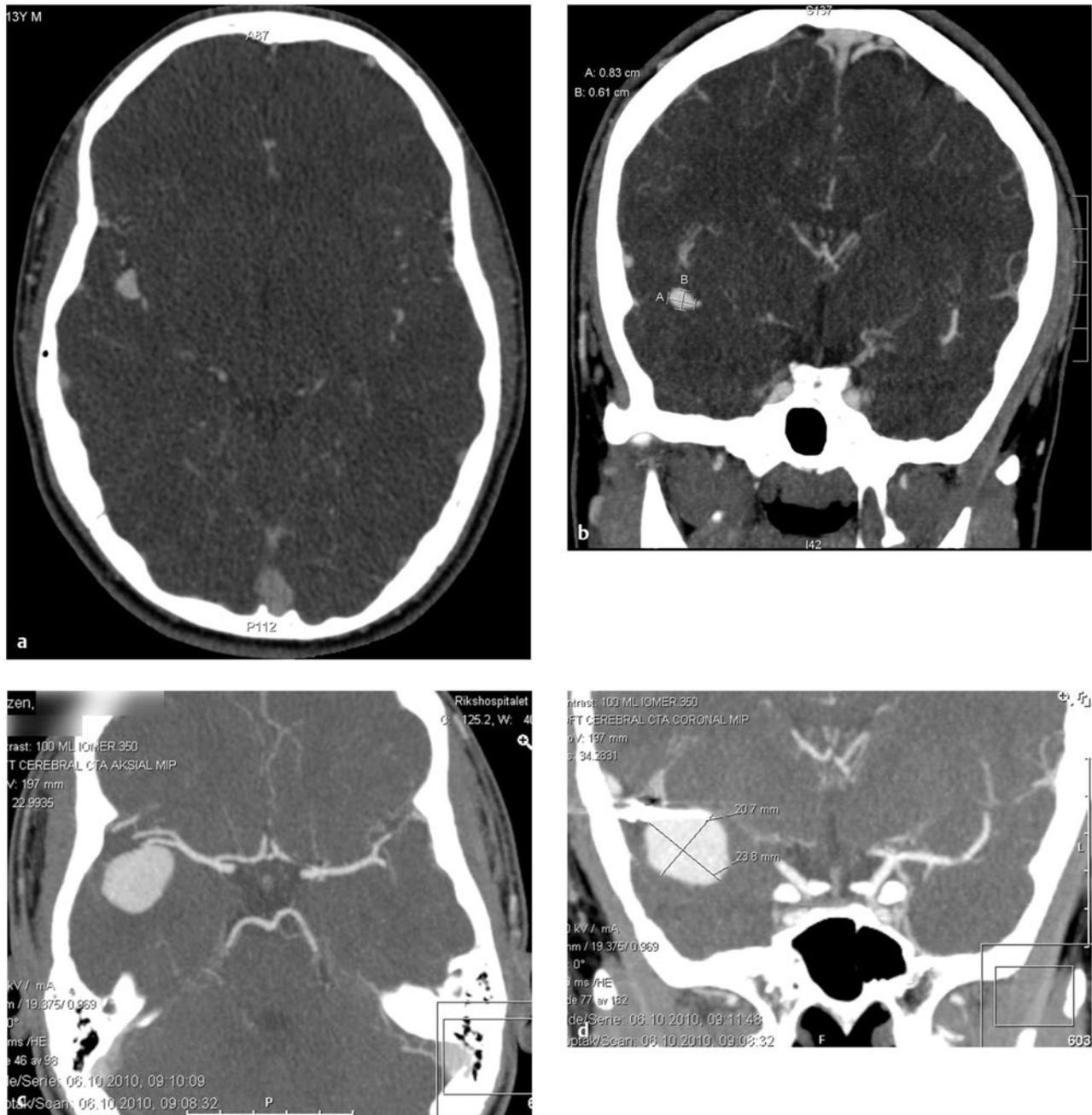


Fig. 66.3 This 15-year-old boy presented with a recurrent, giant distal middle cerebral artery (MCA) aneurysm. (a,b) He had presented 2 years earlier with a small MCA aneurysm arising from a bifurcation in the superior division of the MCA along the insular M2 segment. He underwent right pterional craniotomy and direct clipping in Norway, with no surgical complications. (c,d) Follow-up revealed aneurysm recurrence with marked enlargement, (e,f) as seen on computed tomographic angiography (*continued*)

in the series. Aryan et al¹¹ reported an 8% rate of intraoperative perforator injury, and Sharma et al⁷ reported a 2% rate. Perforators may be densely adherent to the aneurysm dome or may be hidden behind the aneurysm. After aneurysm clipping, we use indocyanine green video angiography to assess perforator and large branch patency. Aneurysms originating from parent arteries that have associated perforators must be meticulously inspected after permanent clipping to be certain that all

perforators have been excluded from the clips, which often requires aneurysm puncture and deflation to improve the view.

66.5.2 Postoperative Complications

In our series, there was 1 case of transient postoperative neurologic worsening and 1 case of permanent neurologic deficit.⁵ There were no mortalities. In the literature, postoperative

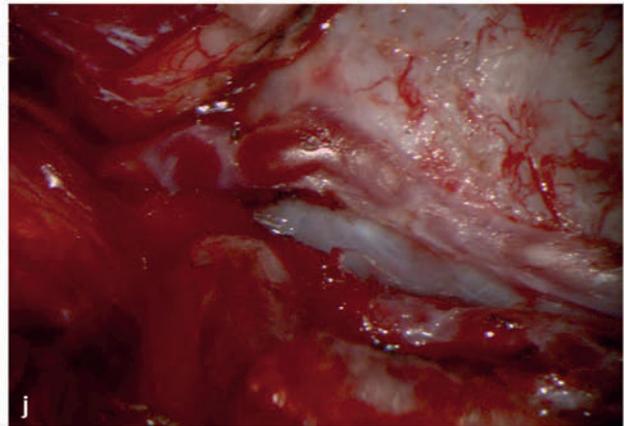
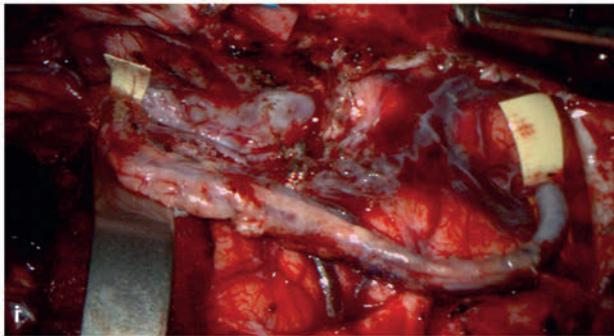
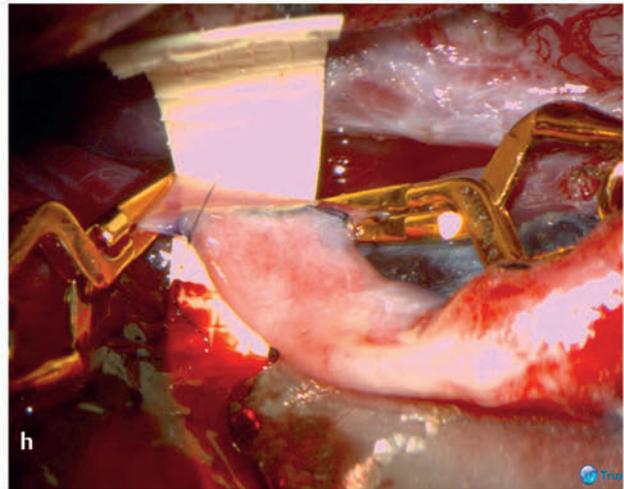
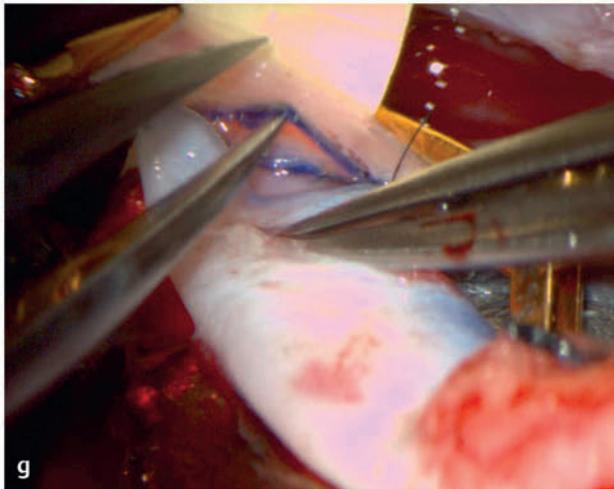
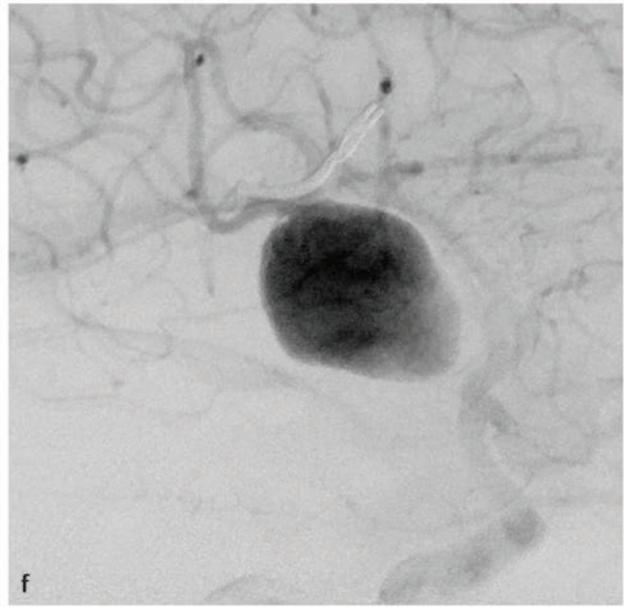
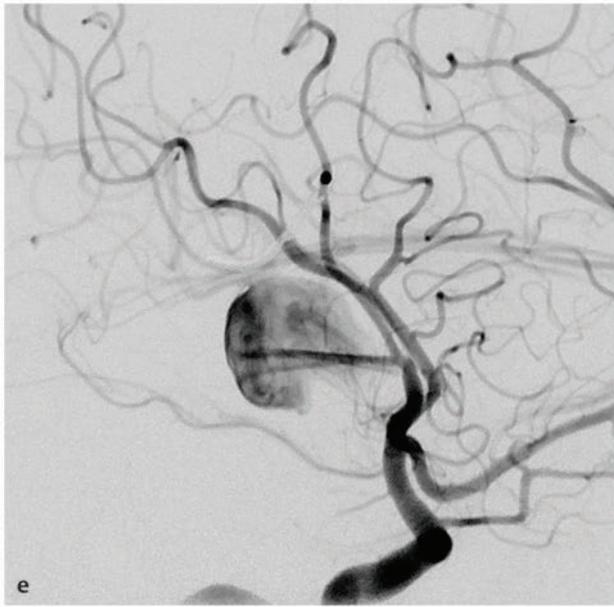


Fig. 66.3 (continued) and catheter angiography. (g,h) This aneurysm was treated with a bypass from the superior trunk of the MCA (i) to the efferent angular artery. (j) The aneurysm was then occluded proximally, but a branch of the inferior trunk adhered to the aneurysm wall. (continued)

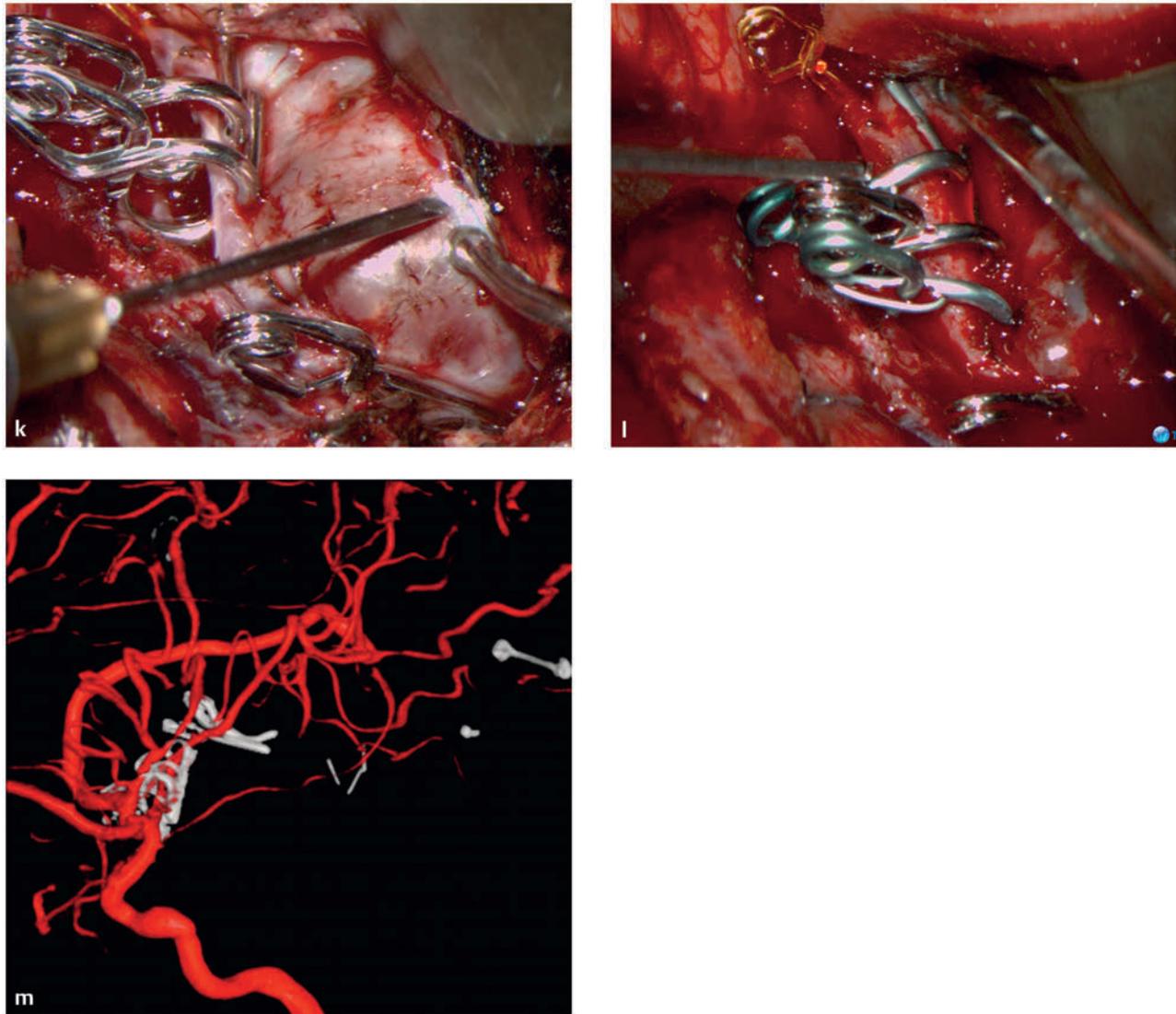


Fig. 66.3 (continued) Tandem fenestrated clips were used to reconstruct this adherent branch, but (k) suction decompression and (l) repositioning of the clips were required. (m) Postoperative angiography with three-dimensional reconstruction confirmed patency of all trunks and branches.

mortality after the surgical treatment of pediatric intracerebral aneurysms is also rare, ranging from 2 to 5%,^{3,7,11,17,19,20} as is postoperative aneurysmal rebleeding. Kakarla et al¹⁷ reported a 2% rate, and Meyer et al³ reported a 4% rate. Aryan et al¹¹ reported a 6% rate of postoperative stroke, an 8% rate of new hemiparesis, and a 6% rate of new cranial nerve deficits. There was a 4% rate of wound infection. Kakarla et al reported a 4% rate of stroke and a 6% rate of new postoperative neurologic deficits, including 2 new cranial nerve deficits.¹⁷ In the immediate postoperative period, they reported 1 epidural hematoma and 1 cerebellar hematoma, both of which required surgical evacuation. Occlusion occurred in 2 of 13 bypasses in the perioperative period. Sharma et al⁷ reported a 4% rate of postoperative stroke.

Although not a surgical complication, hydrocephalus develops in many patients with subarachnoid hemorrhage, and CSF diversion procedures are required. Careful attention must be paid postoperatively to signs and symptoms of hydrocephalus. It is generally thought that chronic hydrocephalus after subar-

achnoid hemorrhage results from the fibrosis of arachnoid granulations in response to the presence of blood products and subsequently impaired CSF resorption. As this is not an obstructive problem, we treat hydrocephalus related to subarachnoid hemorrhage with ventriculoperitoneal shunting, not endoscopic third ventriculostomy. Infectious meningitis is also a potential complication, related to either the surgical procedure or external ventricular drainage, and it must be detected and treated.

Although not a postoperative complication, delayed aneurysm recurrence is a concern in pediatric patients because of the dysplastic nature of some of these aneurysms, and also because of the long life expectancy of the patients. Postoperative catheter angiography is mandatory after treatment to confirm complete aneurysm occlusion. Furthermore, follow-up MR angiography is recommended annually for the first 5 years after treatment. The frequency of MR angiography can then be decreased to once every 5 years if no residual or new aneurysm is detected. For pediatric patients with multiple aneurysms,

continued angiographic surveillance throughout life is warranted to identify new aneurysms that may develop later in adulthood. We aggressively treat unruptured aneurysms that are identified in patients with previous subarachnoid hemorrhage, in accordance with the International Study of Unruptured Intracranial Aneurysms (ISUIA) recommendations. Furthermore, we aggressively treat de novo aneurysms because they are likely to be less stable and carry a higher risk for rupture than small, stable aneurysms that are incidentally diagnosed.

As mentioned above, angiographic vasospasm after intracerebral aneurysm is less common in children than in adults. Clinically significant vasospasm requiring therapy is even rarer. In a child with an acute neurologic change and suspected vasospasm, an emergent CT scan of the head should be obtained to rule out a surgical lesion such as an epidural hematoma. In the absence of this, “triple H” therapy should be immediately instituted: hydration with intravenous normal saline, hemodilution, and hypertension with vasopressors such as phenylephrine if needed. Vascular imaging should be considered. Our preference is catheter angiography because it provides the best resolution of the blood vessels and allows the opportunity to treat areas of stenosis with intra-arterial verapamil or angioplasty. At our institution, patients with subarachnoid hemorrhage and poor neurologic examinations are followed with daily transcranial Doppler studies. Elevated velocities prompt catheter angiography.

66.6 Treatment Alternatives

66.6.1 Observation

In a series of 59 pediatric patients with aneurysms, 8 aneurysms were observed to undergo spontaneous thrombosis and did not require further treatment.¹⁴ Liang et al demonstrated 2 cases of spontaneous thrombosis in a total of 24 patients.⁶ The primary reason for observation was the high risk for neurologic decline expected after treatment, although the specific risks were not defined. Unfortunately, the literature does not offer ways to predict which patients will do well with observation. In our institutional series, 18 patients with multiple areas of long-segment dysplasia that were unruptured were managed conservatively with observation.⁴ Interestingly, there were no events of bleeding during the observation period. Two aneurysms demonstrated subtle enlargement. One required endovascular coiling and one required endovascular balloon occlusion of the parent artery. Additionally, one demonstrated significant enlargement and underwent stent coiling. Therefore, because of the high risk for aneurysm enlargement and/or rupture, we strongly recommend the direct treatment of pediatric aneurysms. We do not advise observation for pediatric patients who have ruptured aneurysms or who have large or giant aneurysms with symptomatic mass effect. Small aneurysms less than 7 mm in diameter can be observed with serial imaging, but enlarging aneurysms should not be observed, even when they are less than 7 mm in diameter. Patients with long-segment dysplasia that is unruptured may be observed because this finding may not represent true aneurysm pathology, and it is associated with a benign clinical course in our experience. Children

who have other conditions associated with intracranial aneurysms, such as microcephalic osteodysplastic primordial dwarfism (MOPD) type 2, should be followed vigilantly for life.²¹

66.6.2 Endovascular Treatment

In our institutional series of 77 pediatric patients (defined as age less than 19 years) with intracerebral aneurysms, 19 underwent endovascular coiling as the primary treatment modality.⁴ There was one arterial injury related to the procedure, with subsequent cerebral infarction and monoparesis. There was one intraprocedural aneurysm rupture, which was treated endovascularly without sequelae. Three residual aneurysm remnants required treatment. One was treated with repeated coiling, one was treated with stent-assisted coiling, and one was taken to the operating room for aneurysm trapping and extracranial–intracranial bypass. There was one death due to rupture of a de novo aneurysm 20 months after primary treatment.

For some extensive fusiform aneurysms and very large saccular aneurysms deemed not amenable to either surgical clipping or endovascular coiling, parent artery occlusion can be considered. It is critical to first demonstrate adequate collateral circulation angiographically and, when possible, with awake balloon test occlusion. Hetts et al reported 11 such patients from our institutional series.⁴ All complications were transient: one hemiparesis, one monocular vision loss, and one sixth cranial nerve palsy. Three patients developed de novo aneurysms, two of which required surgical trapping and bypass. The third was stable with observation.

There is currently no consensus to guide the decision whether to treat patients microsurgically or endovascularly. Some argue that patients with aneurysms located at the basilar tip should be preferentially referred for endovascular coiling.¹⁰ Lasjaunias et al reported a series of 17 patients treated for fusiform aneurysms, of which 14 were treated endovascularly, suggesting their support of endovascular techniques for this type of morphology.¹⁴ Eleven patients underwent parent artery occlusion, two underwent proximal occlusion, and one underwent coiling.

We compared primary endovascular treatment and primary microsurgical treatment with respect to treatment durability.⁵ In comparison with our microsurgical results, we reported a 79% complete obliteration rate with endovascular treatment, as well as a 19% recurrence rate and a 19% de novo aneurysm formation rate (► Fig. 66.4a–i).⁵ Endovascular therapy offers good treatment options in selected aneurysms with favorable anatomy. Patient and parent preferences must be considered in the selection of a treatment modality, with a critical eye on efficacy and long-term durability. In general, endovascular therapy has greater parental appeal and slightly lower associated risks, but surgery has greater efficacy, durability, and protection against rebleeding.

66.7 Prognostic Factors

The small numbers included in currently available series limit our ability to identify prognosticators definitively. In patients

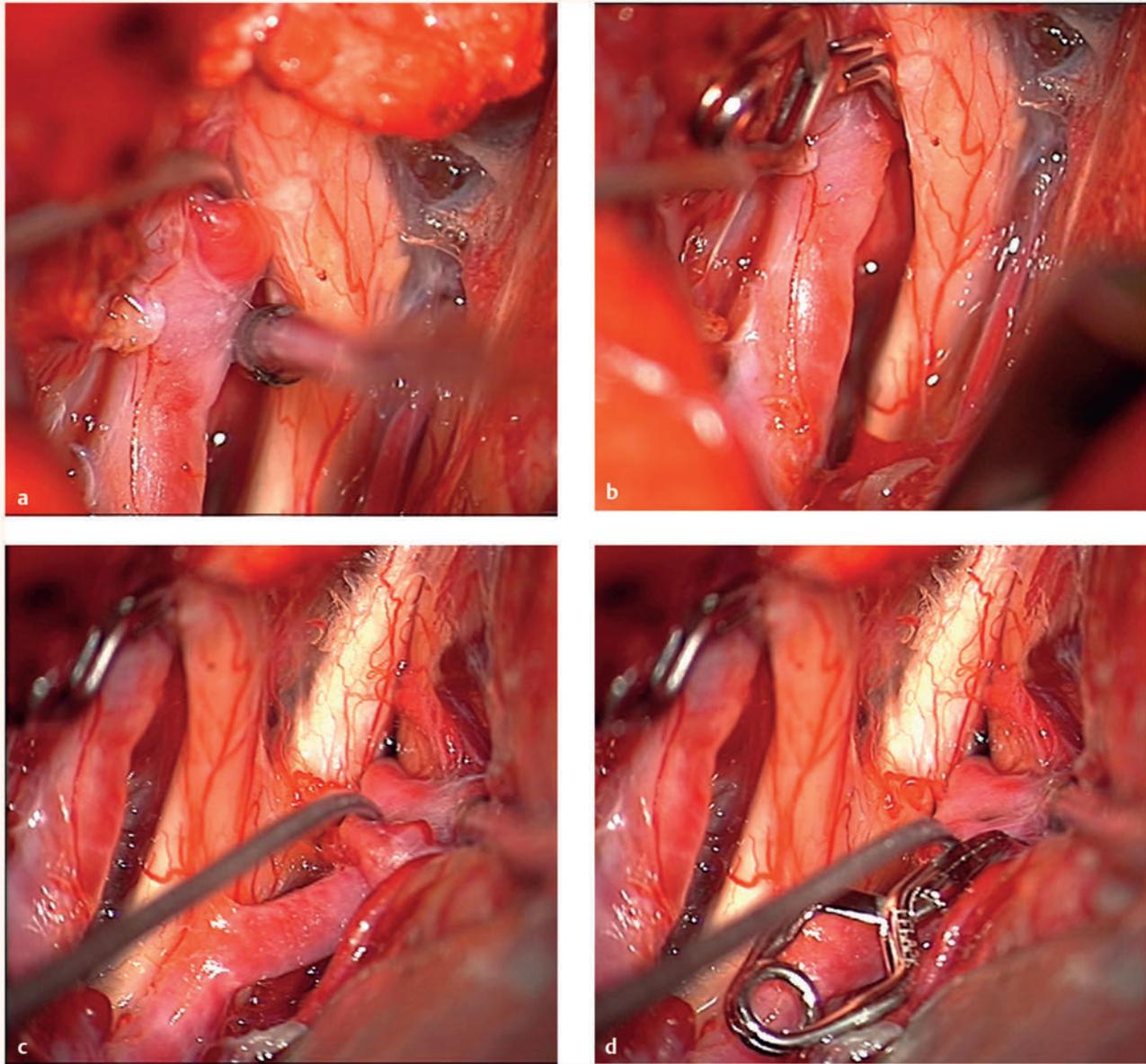


Fig. 66.4 This 14-year-old girl with sickle cell disease had a subarachnoid hemorrhage from a left superior cerebellar artery aneurysm and was treated with endovascular coiling. Surveillance angiography demonstrated enlargement of other aneurysms and de novo aneurysms. She underwent left pterional craniotomy for clipping of these multiple aneurysms. (a) The ophthalmic artery aneurysm was exposed after anterior clinoidectomy and (b) clipped with a side-angled clip. (c) Her small anterior communicating artery aneurysm (d) was clipped (*continued*)

who present with subarachnoid hemorrhage, the preoperative clinical grade appears to correlate with outcome. Storrs et al reported that patients who presented with a worse grade after subarachnoid hemorrhage had worse outcomes after surgery.¹² Likewise, Sharma et al noted that 90% of the patients who pre-

sented with a Hunt and Hess grade of 1 through 3 had good outcomes, and nearly 70% of those who presented with a grade of 4 or 5 had poor outcomes.⁷ Proust et al reported excellent outcomes in 85% of patients presenting with Hunt and Hess grade 1 through 3 subarachnoid hemorrhages.⁸

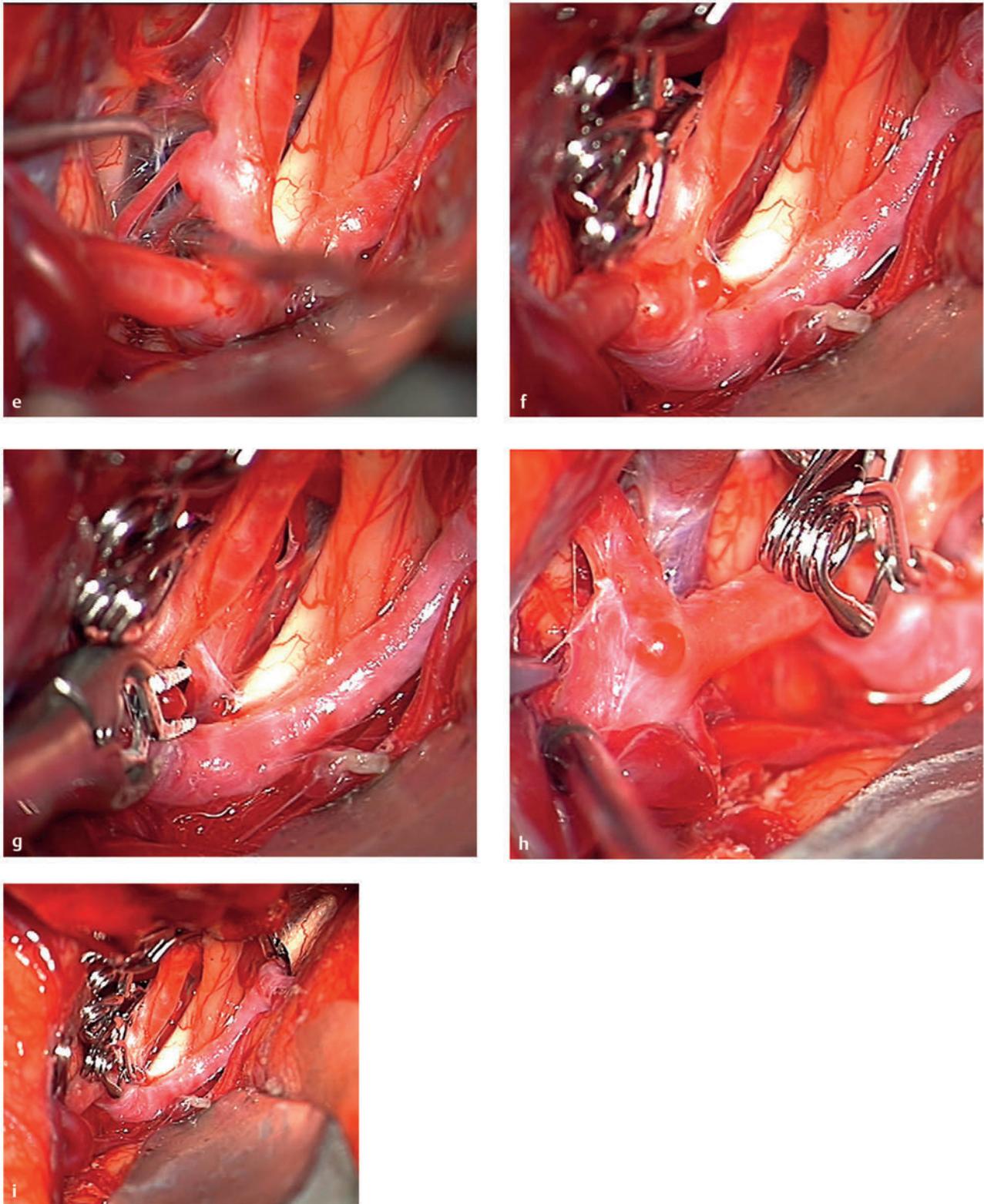


Fig. 66.4 (continued) (e) as were posterior communicating, anterior choroidal, (f,g) internal carotid artery bifurcation, and(h) middle cerebral artery aneurysms. All aneurysms were small and very thin-walled. (i) One craniotomy accessed all six aneurysms.

Pearls

- When a pediatric patient presents with an aneurysm, the dynamics of selecting a treatment modality are considerably different from those for an adult with a similar lesion.
- Although concerns for safety and efficacy remain a priority, the issue of durability of treatment takes on new meaning for a child with five to seven decades of life remaining.
- In our experience, the complication rates, morbidity, and mortality of operative versus endovascular treatment have been comparable. With respect to efficacy, both modalities have also been comparable.
- In regard to durability, however, the increased recurrence rate demonstrated in the endovascular treatment population, even after a modest follow-up period, warrants serious consideration. Furthermore, the incidence of delayed complications from de novo aneurysm formation was considerably higher in the patients who underwent endovascular treatment. These results of endovascular treatment inevitably led to additional therapy, often in the form of definitive microsurgical treatment.
- Although the intrinsic appeal of endovascular therapy to parents must be recognized and respected, parental bias must be tempered by a serious consideration of therapeutic durability, the potential for delayed complications, and the need for additional treatment later in life.
- By these criteria, microsurgical intervention may be superior to endovascular treatment because the long life expectancy of pediatric patients requires us to redefine our concept of treatment permanence.
- At present, with little evidence in children, the treatment of symptomatic vasospasm follows the adult guidelines of “triple H” therapy with hydration, hemodilution, and hypertension.

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67 Pediatric Arteriovenous Malformations

Edward R. Smith

Vascular malformations of the central nervous system are a heterogeneous group of lesions that occur in both the brain and the spinal cord. Like those in other anatomical sites, vascular anomalies of the central nervous system can be classified according to rheologic characteristics (fast-flow and slow-flow) and by channel composition (i.e., arteriovenous malformation [AVM], cavernous malformation [CM], and venous malformation [VM]) and may occur either independently or in association with syndromic conditions. AVM is arguably the most important vascular anomaly in the nervous system in children; it is relatively common and usually requires treatment given the risk for hemorrhage.

67.1 Pathophysiology

AVMs consist of direct arterial-to-venous connections without intervening capillaries; they occur in the cerebral hemispheres, brainstem, and spinal cord. Functional neural tissue does not reside within the lesion.¹ Anomalies range from simple arteriovenous fistulas to complex tangled channels connecting enlarged feeding arteries to draining veins.

AVMs may increase in size over time or may demonstrate changes in the caliber of component vessels, which may portend a risk for hemorrhage. These changes may occur from “mechanical” dilation as the result of increased flow through poorly differentiated vessels and the recruitment of collateral arterial feeders. Ischemia and surrounding microhemorrhages with resultant gliosis may promote the enlargement of an AVM by destruction of the surrounding parenchyma. Expansion of an AVM may also result from the growth of new blood vessels (i.e., angiogenesis, which is a complex process regulated by a wide range of proteins, including metalloproteinases and related growth factors, such as vascular endothelial growth factor).²⁻⁸ Enlargement of an AVM seems to alter the adjacent brain. Functional magnetic resonance (MR) imaging data have suggested that the presence of an AVM in an eloquent area of the brain may be associated with “migration” of the function to adjoining cortex or to the homologue on the contralateral hemisphere.^{9,10} This migration or displacement of functional neuronal tissue has important implications for surgical planning.

67.2 Epidemiology

AVM is the most common symptomatic high-flow intracranial vascular abnormality in adults and children.¹¹ In a large autopsy series, the overall frequency of detection for AVMs was 1.4% (46 of 3,200 cases of brain tumor).¹² In another report, the annual incidence of symptomatic AVMs was 1.1 per 100,000.¹³ The pediatric age group accounts for 12 to 18% of all AVMs from major centers, and the overall prevalence in children is about 0.02%.¹⁴⁻¹⁷ Most AVMs present in adulthood, with a mean age of patients at presentation of approximately 30 to 40 years. About 20% of all symptomatic AVMs present before 15 years of age.¹⁸ There is no sex predilection for pediatric AVMs. A number

of AVMs are associated with underlying genetic conditions. The *RASA1* mutation, resulting in familial AVMs and/or cutaneous capillary malformations, has been associated with symptomatic cerebral AVMs in a small number of families.¹⁹ Hereditary hemorrhagic telangiectasia is a genetic condition that predisposes affected individuals to AVMs. Thirty-five percent of pediatric cases were associated with hereditary hemorrhagic telangiectasia. Twenty-three percent of patients had multiple AVMs, with a mean age at presentation of 35 years¹³

67.3 Presentation

The neurologic signs and symptoms of central nervous system vascular anomalies correlate with the anatomical site of involvement and the age at presentation. The lesions can be deep in the parenchyma, superficial, or located in the dural and arachnoid coverings. In general, AVMs that are symptomatic at or soon after birth are extremely fast-flow lesions and often are associated with high-output cardiac failure. The more common pial AVMs usually present with hemorrhage later in childhood or adulthood. The likelihood and severity of symptoms and the probability of hemorrhage caused by the vascular anomaly depend on multiple factors, including type of malformation, size, location, and hemodynamic and angioarchitectural characteristics.

Hemorrhage and seizure are the most common presenting symptoms of pediatric AVM, but the findings may also include headache, focal neurologic deficits, and cognitive decline.²⁰⁻²³ A substantially large number may be asymptomatic.

Children with AVM are more likely than adults to present with intracranial hemorrhage: 80 to 85% in some pediatric series.^{15,24} For children known to have an AVM, the annual risk for hemorrhage has been estimated at 2 to 4%.^{25,26} Hemorrhagic events from an AVM in childhood have been associated with a 25% mortality rate.²⁷ In contrast to earlier reports suggesting that smaller AVMs may be associated with a higher risk for bleeding, more recent data have shown that size is not a major determinant in the risk for hemorrhage.^{28,29}

The hemorrhage can produce seizures, headache, or focal neurologic deficits. The bleeding associated with an AVM is most often an intraparenchymal hemorrhage, although subarachnoid hemorrhage and intraventricular hemorrhage are also common. Bleeding can occur in any one location or in all three sites together.³⁰⁻³² A nontraumatic intraparenchymal hemorrhage in a child should raise concerns for the presence of an AVM or tumor. Rates of rebleeding have been reported to be approximately 6% within the first 6 months.

Independently of hemorrhage, AVMs can produce deficits from mass effect or from cerebral ischemia that is due to the diversion of blood to the AVM from the normal cerebral circulation (“steal”). The presentation of symptoms in AVM is generally acute if related to hemorrhage or seizure (often occurring within minutes to hours) but is chronic (over months) if related to a steal phenomenon or headache.

67.4 Physical Signs

Systolic bruits over the eye or through the head and or fontanelles are suggestive of an AVM; focal neurologic signs help localize the lesion. A bruit is found in 15 to 40% of patients with AVM. It is especially common if branches of the external carotid arteries are involved and best heard over the ipsilateral eye or mastoid region. Large, pulsatile vessels may be present in the scalp, face, and neck, and vascular anomalies can be found in retina. Major arteriovenous shunting may also be associated with tachycardia, cardiomegaly, and even cardiac overload, especially in infants and children and particularly when the vein of Galen is involved. Other than potential neurologic deficits, the typical patient will not have any obvious findings on general physical examination to suggest an underlying AVM.

67.5 Imaging

The comprehensive evaluation of a patient with an AVM includes a detailed history, neurologic and physical examination, and radiographic studies to delineate the anatomy of the lesion.³³ The vast majority of patients present with the new onset of a neurologic deficit, such as an unusually severe headache (“worst headache of my life”) or seizure due to acute hemorrhage. These patients should be screened with computed tomography (CT) (► Fig. 67.1, ► Fig. 67.2). CT is a reliable indicator of recent intracranial hemorrhage, may permit localization of the source of bleeding, and facilitates the early diagnosis of

AVM. Because of its speed, availability, and ease of use, CT angiography has increasingly been employed as an initial study upon presentation to the emergency department.³⁴ CT angiography better delineates AVM, particularly in the setting of an acute hemorrhage. In addition, the index of suspicion for an AVM is high whenever an intraparenchymal hemorrhage is found in a child or young adult without an antecedent history of trauma.³⁵ Repeated imaging in 4 to 6 weeks is indicated to evaluate the hemorrhagic cavity after the clot has cleared.³⁶

Infratentorial AVM typically appears as a heterogeneous area of mixed density with serpiginous areas of enhancement after the infusion of contrast material. Cerebral atrophy may sometimes be seen on the affected side. A large malformation or an intracerebral hematoma may distort the normal intracranial anatomy. A hematoma from AVM can be situated in the cortex or adjacent white matter, so that it usually can be distinguished from a hypertensive hematoma, which is often deeply placed. Intraventricular extension of the hematoma is common.

MR imaging is also useful in the diagnosis and delineation of the anatomy of AVM (► Fig. 67.1). MR imaging better localizes the parenchymal structures relative to the AVM, even if there is a strong suspicion of AVM based on the CT or CT angiographic findings and angiography is planned. The typical MR imaging appearance is that of a latticework of signal-void spaces highly contrasted against the surrounding cerebral tissue on both T1- and T2-weighted sequences. These are intermixed with regions

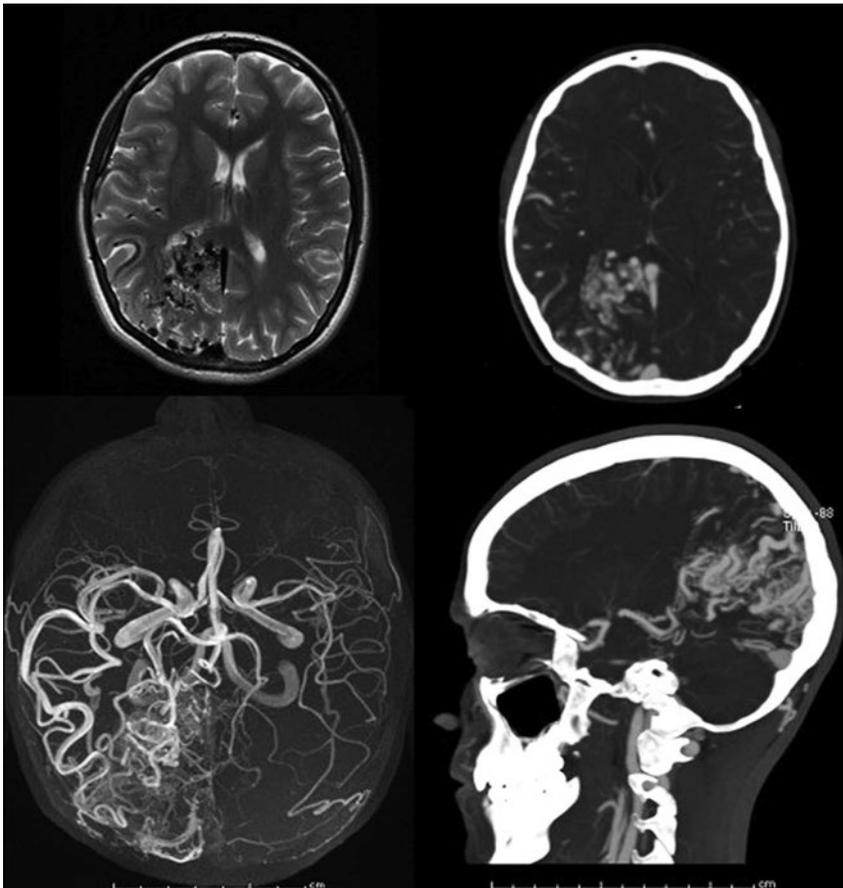


Fig. 67.1 Characteristics of an arteriovenous malformation on magnetic resonance (MR) imaging and computed tomography (CT). Upper left: Axial T2 MR image with dark flow voids evident in the right occipital pole. Upper right: Same lesion detailed by CT angiography. Lower right: Sagittal view of the lesion, demonstrating a wedge-shaped configuration. Lower left: A collapsed MR angiogram.

of various signal intensities corresponding to blood products in different stages of evolution and occasionally calcium and hemosiderin.^{37,38} The serpiginous shape of the vessels may be distinctive, identified as flow voids, and the relevant anatomy can be well visualized with MR angiography. Susceptibility imaging will sometimes disclose evidence of previous

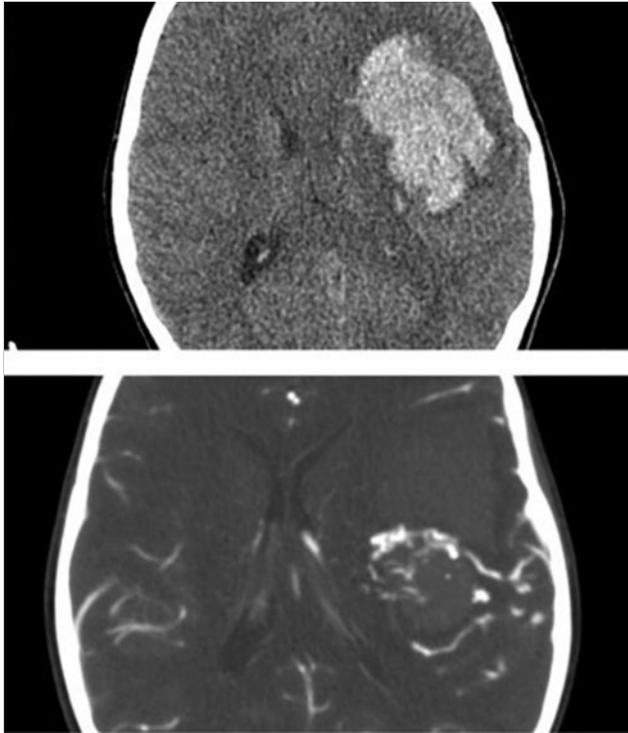


Fig. 67.2 Utility of computed tomographic (CT) angiography in an emergent setting. Upper image is a noncontrast axial CT scan showing a large left frontal hemorrhage. Lower image is a CT angiogram of the same patient revealing the relationship of an arteriovenous malformation to clot and serving to increase the safety of emergent clot removal.

hemorrhage as a dark “bloom” around the nidus.³⁹ Chronic ischemic changes, presumably a result of the “steal” phenomenon or venous hypertension, may be identified on MR imaging as bright signal of the surrounding brain on FLAIR (fluid-attenuated inversion recovery) or T2 images. The understanding of local ischemia can also be improved with diffusion–perfusion imaging.⁴⁰

Traditional digital subtraction angiography remains the definitive investigative technique for the evaluation of intracerebral AVM (► Fig. 67.3). It establishes the nature and extent of the lesion, in addition to its blood supply and venous drainage.⁴¹ Angiography generally includes bilateral injection of both the internal and external carotid arteries and the vertebral arteries in order to visualize all of the vessels supplying the AVM. Three-dimensional angiography with computer-generated reconstruction is increasingly employed to depict lesional anatomy. It is important to underscore that 15% of cerebral AVMs receive some blood supply from the ipsilateral or contralateral meningeal arteries.⁴²

The typical angiographic appearance of an AVM is that of distended, tortuous afferent and efferent vessels connecting with a tangled vascular mass, through which the circulation time is rapid (i.e., arteriovenous shunting). Angiography can fail to demonstrate an AVM despite suggestive findings on CT or MR imaging, usually because of the partial or complete thrombotic occlusion of feeding vessels. Other suggested causes of an angiographically occult AVM include small size, compression by adjacent clot, and destruction by hemorrhage. In the setting of an intracerebral hematoma without a clearly proximate cause, repeated MR imaging at 6 weeks after a hemorrhage is often recommended to screen for an occult AVM.^{35,36}

For those patients presenting with seizure, electroencephalography can be considered during the initial evaluation. Electroencephalography may show focal or lateralized abnormalities that suggest the presence of an underlying structural lesion. These findings should prompt further investigation, most commonly MR imaging.

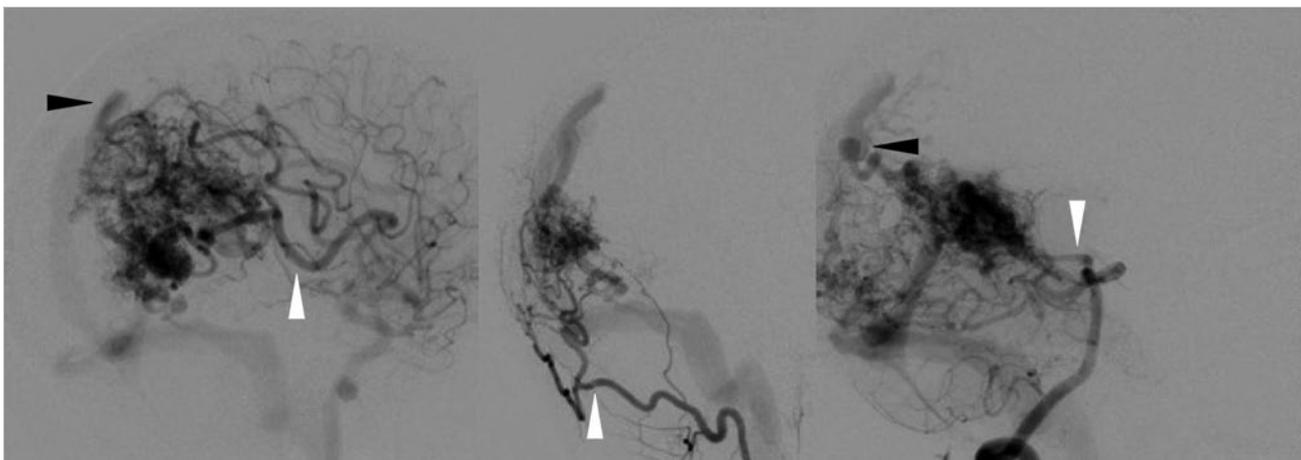


Fig. 67.3 Angiographic characteristics of arteriovenous malformation (AVM). Catheter angiography of the AVM from ► Fig. 67.1 reveals feeding arteries (*white arrowheads*) and draining veins (*black arrowheads*). Images include (from left to right) internal carotid artery, external carotid artery, and vertebrasilar injections. These studies highlight the need to perform multiple-vessel injections to identify all potential lesional vessels.

67.6 Indications for Surgical Treatment

67.6.1 Rationale for Intervention

The reasons for treating an AVM, particularly in children, are compelling. With each hemorrhage from an AVM, there is an approximately 25% chance that a permanent deficit or death will result, and children have an annual risk for hemorrhage of about 2%, a substantial cumulative risk for younger individuals with an expected long life span.⁴³ Treatment has the potential to reduce or eradicate the lifetime risk for hemorrhage and also has the potential to eradicate AVM-related comorbid conditions, such as seizures and neurologic deficits. The goal of therapy is complete obliteration of the AVM. Partial destruction does not confer protection from bleeding in the future.³³

In general, there is a consensus that intervention for patients with symptomatic lesions—particularly AVMs that have bled—is warranted. More difficult are those lesions that are found incidentally or that cause questionable symptoms. In these cases, the indications for treatment rest on weighing the risk of intervention against the risk of the natural history of the unruptured AVM. As discussed above, the risk for hemorrhage is incompletely understood, although some data suggest that AVMs in younger children are more likely to bleed over the course of a lifetime, increasing the impetus to treat. In addition to these studies, one can review the specific angioarchitecture of an individual lesion. Recent work has revealed that angiograms of pediatric AVMs can identify features that are associated with an increased risk for bleeding. Smaller AVM size, exclusively deep venous drainage, and an infratentorial location are specific angioarchitectural factors independently associated with an initial hemorrhagic presentation in children with AVMs, and the presence of these factors, even in an asymptomatic patient, may help to inform the decision to treat in selected cases.⁴⁴

The optimal management of AVMs is controversial in both adults and children. AVM can be treated by one of three modalities—resection, endovascular techniques, or radiosurgery—or with a combination of embolization and either radiation or surgery. Each has inherent benefits and limitations. For some complex lesions, such as those with a high (4 or 5) Spetzler-Martin grade (see below), careful observation may be the appropriate option. The wide variety of lesional anatomical features and patient risk profiles, coupled with the lack of standardized outcome measurements, makes comparisons among studies difficult, reflected by the minimal information provided in the recent American Heart Association guidelines for the management of stroke in children.⁴⁵ Outcome measures include the following: (1) radiographic obliteration of the lesion; (2) observer outcome scales (Rankin Scale or Glasgow Outcome Scale); (3) patient-generated quality-of-life data; and (4) rates of specific comorbid conditions (e.g., seizures, headaches). The objective of this section is to offer guidance on when to select surgical treatment and how to provide the best operative management of these lesions.

67.6.2 Goals of Surgical Treatment

The operative goal is complete removal of the lesion. The decision to resect an AVM is based on several factors: (1) eloquence

Table 67.1 Spetzler-Martin arteriovenous malformation grading system

Size	Points
0–3 cm	1
>3–6 cm	2
>6 cm	3
Location	
Non-eloquent cortex	0
Eloquent cortex	1
Deep venous drainage	
Not present	0
Present	1

of the cortical location (speech, motor function, sensation); (2) pattern of venous drainage; (3) size; (4) associated aneurysms; (5) recent hemorrhage; (6) clinical deterioration; and (7) risk for complications from other modalities of therapy (e.g., radiation injury to the developing brain).^{46,47} Several of these factors are combined in the Spetzler-Martin⁴⁸ grade, which incorporates eloquence of location, pattern of venous drainage, and size and is considered predictive of the outcome of surgical management (► Table 67.1).

67.6.3 Indications for Surgical Treatment of Simple Lesions (Low Spetzler-Martin Grade)

A series of 20 pediatric patients with Spetzler-Martin grades 1 to 3 AVMs were treated by resection.⁴⁹ Good recovery was achieved in 18 of 20 children (90%), and 1 death (5%) was related to prior hemorrhage. In addition to the clinical findings, radiographic outcomes were also evaluated; the radiographic obliteration rate was 89% (17 of 19). In another study, lesions with a low Spetzler-Martin grade were successfully treated by resection, whereas high-grade lesions were treated by radiosurgery.⁴⁷ Other investigators have also recommended resection for low-grade or small, surgically accessible lesions, citing the benefits of immediate protection from rebleeding and the avoidance of delayed radiation-related brain injury. At the same time, they caution about the need for further study of the indications for surgical intervention.⁵⁰

The safety and efficacy of resection are increased by preoperative embolization in selected patients, especially both children and adults with larger lesions.^{51–54} Preoperative embolization can reduce blood loss, shorten operative time, occlude vessels less accessible to the surgeon (e.g., deep feeding arteries), and decrease the size of the AVM.³³ Nevertheless, no prospectively controlled studies have compared resection with and without embolization.

Although randomized trial data are lacking, the combined literature of institutional experience strongly supports resection as a primary treatment for children with Spetzler-Martin grade 1 or 2 AVMs. The low postoperative morbidity rates in patients with low-grade lesions (ranging from 0 to 12%), along with high rates of complete obliteration (up to 100%), suggest that

delayed control, inherent to radiosurgery, may not be warranted.^{24,47,49,55} For comparison, a similar group of patients treated with radiosurgery alone had a reported 80% efficacy rate of lesion obliteration at 36 months, with 4 of 53 patients having recurrent hemorrhage after treatment.⁵⁶

67.6.4 Indications for Surgical Treatment of Complex Lesions (High Spetzler-Martin grade)

Complex lesions (as defined by a higher Spetzler-Martin grade) carry a substantially greater risk for children. Multimodality therapy of AVM has been advocated by several investigators.^{24,47,57,58} Neurointerventionalists, radiation oncologists, and neurosurgeons work together to determine the best strategy for a particular patient. With the use of a multimodality approach, angiographic obliteration rates of 92.9% have been reported. In carefully selected patients treated with resection alone, a cure rate of 100% has been achieved.⁴⁷

The decision process becomes controversial for patients with high-grade lesions. Preoperative embolization has been employed to decrease flow and occlude deep feeding vessels, maneuvers particularly helpful to facilitate resection. Embolization is rarely employed as the sole treatment for AVM, although the agent Onyx (Micro Therapeutics [Covidien], Mansfield, MA) has recently been used.^{50,59} Radiosurgery alone seems to protect against bleeding following radiographic obliteration. Others have argued that there is some protective effect even before total radiographic obliteration of the lesion.^{60,61}

In one report, outcomes following resection with or without adjunctive embolization were 100% excellent or good at 36 months.⁴⁷ These results are possible because some patients were excluded if they were considered to be poor surgical risks. Embolization can reduce the size of an AVM, making it more amenable to radiosurgery.⁵⁹ In patients treated with radiosurgery without embolization, overall outcomes of 91% excellent or good and mortality of 9% were attained. When embolization was used before radiosurgery, the outcomes improved to 100% excellent or good at 36 months.⁴⁷ The efficacy of the multimodality treatment of large, complex lesions is supported by the results in a group of 53 children, in whom a 58% cure rate was noted at 3-year follow-up for those with AVMs larger than 6 cm in diameter.⁶²

In summary, the high likelihood of obliteration, coupled with low complication rates, makes a convincing argument in favor of multimodality treatment of pediatric AVMs. It is our practice at Boston Children's Hospital to review cases in a multidisciplinary meeting to weigh the risks and benefits of intervention for AVMs. In general, high-grade lesions are treated only after a detailed review and a discussion of alternatives and risks with the family. It is not unusual to recommend observation for children with larger, high-risk AVMs (often defined as those with a Spetzler-Martin grade of 5 or 6).

67.7 Surgical Treatment

Once the decision to operate has been made, a series of steps are followed that involve the timing of the operation, perioperative management, and specific operative strategies. Although

the marked variations in the size, location, and presentation of AVMs in the pediatric population preclude the possibility of a single, stock approach to all lesions, core principles remain that can reduce the risks of surgery. These key points are summarized in this section.

67.7.1 Timing of Treatment

The urgency of treating an AVM depends on its presentation. In the case of asymptomatic lesions, treatment planning can proceed in an elective fashion because the hemorrhagic rate is relatively low, approximately 1 to 3% per year for an unruptured AVM. In the case of lesions that have bled, rebleeding rates are approximately 6% for the first 6 months and 3% per year afterward.^{20,63}

The treatment of an AVM that has already bled depends on the clinical findings and on the anatomy of the malformation. Elevated intracranial pressure may preclude definitive imaging of the lesion. Urgent surgical intervention is necessary if the child is acutely ill from a focal clot or from hemorrhage-related hydrocephalus. If formal angiography is not possible (because of the clinical presentation), then more rapid imaging of the vasculature, such as with CT angiography, is necessary for preoperative planning.⁶⁴

The surgical alternatives are decompression of the cranial vault by evacuation of clot and/or cerebrospinal fluid diversion to lower intracranial pressure. In such emergent situations in which the anatomy of the lesion is unknown, given the low rebleeding rates of the lesions, definitive treatment of the AVM can be postponed until the child is clinically stable and the complex anatomy of the AVM can be delineated by formal angiography. Care should be taken to remove clot only, with the vascular malformation left undisturbed. Surgical treatment is usually scheduled at a later time (days to weeks) after ictus, often after better imaging has been obtained.

Preoperative embolization of an AVM assists the surgeon by reducing the size and flow of the lesion. In addition, deep arterial feeders in difficult locations can be treated before craniotomy. Embolization should be scheduled within a short period of time, 0 to 72 hours, before the resection. Longer delay risks the formation of new feeding vessels and collateralization, which can jeopardize resection. (For the same reasons, a similar schedule should be applied for embolization before radiosurgery.)

67.7.2 Perioperative and Anesthetic Considerations

The risk for an AVM bleeding during the induction of anesthesia is unknown, but it is probably low.^{33,65} Proximal arterial AVM-related aneurysms may increase the risk for bleeding due to shifts in blood pressure. Therefore, the goal should be normotension and euvolemia throughout the period of anesthesia.

Perioperative antibiotic administration for 24 hours is recommended. The use of antiepileptic medications and corticosteroids is debatable. Confirmation of complete resection by angiography is recommended, either intraoperatively or in the immediate (24 hours) postoperative period. New postoperative neurologic deficits should be investigated promptly by CT (to

assess for hemorrhage or hydrocephalus) or by diffusion-weighted MR imaging (if ischemia is suspected).⁶⁶

There are concerns specific to the pediatric patient undergoing resection of an AVM. Infants have a physiologically small blood volume; they cannot tolerate even minimal blood loss during a procedure. In addition, the cardiac output can be severely altered.^{67–69} Intravenous (IV) lines should be secured before the operation, and packed red cells must be in the operating room.

At Boston Children's Hospital, we employ a standardized protocol for the operative management of children with AVM. Although it may not suit every institution, or every case, we offer it here as an example of a framework that minimizes variation and error (see box "Operative Management of Children with Arteriovenous M (p.891) alformation").

Operative Management of Children with Arteriovenous Malformation

- Preadmission evaluation and studies
 - MR imaging and MR angiography are performed with appropriate series for frameless stereotaxy.
 - A preoperative patient consultation with interventional neuroradiology, neurosurgery, and anesthesia is arranged.
 - The involved teams (interventional radiology, neurosurgery, anesthesia, nursing, and intensive care unit [ICU] staff) review the specific equipment needs, concerns for the individual case, and expected duration of the treatments.
- Peri-embolization management
 - General anesthesia is induced, including the placement of a radial arterial line, bladder catheter, and appropriate IV access (including large-bore IV lines in anticipation of subsequent surgery). The systolic blood pressure is kept at a normal level or 10 to 20 mm Hg lower (based on age, and in no case above 120 mm Hg).
 - Diagnostic angiography is performed, including superselective catheterization to define feeding vessels followed by embolization (if appropriate). The dose of contrast is limited to 7 mL/kg and the radiation dose to 1 Gy per session. Onyx is administered to a maximal dose of 1 mL/10 lb of patient weight.
 - Following the completion of embolization, children are kept intubated in anticipation of operation the following day. Patients are monitored in the ICU, and blood pressure parameters are maintained as through the embolization. Patients are kept sedated, although anesthesia can be lightened briefly to obtain a limited neurologic examination. Post-embolization imaging is limited to presurgical planning or cases in which specific clinical concerns exist (e.g., abnormal examination, difficulties with embolization).
- Surgical management
 - Patients are brought to the operating room from the ICU as the first case the following day and intubated, with bladder and appropriate-bore IV access as previously described. Particular attention is paid to temperature regulation, especially in smaller children, and a warming device, such as a Bair Hugger (Arizant [3M], Eden Prairie, MN), is commonly employed.
 - Before incision, blood products are delivered to the operating room, the operative microscope is draped, and a minimum of three suctions is made available in the operative field. IV

antibiotics are given. Specific instruments are reviewed, including AVM clips, retractors, and bipolar cautery (in particular, nonstick forceps, such as IsoCool [DePuy Synthes, Raynham, MA], are often employed). Frameless stereotaxy is registered and used to plan the incision. In cases of deep lesions, we often complement frameless stereotaxy with ultrasonography.

- The general principles of AVM resection are followed (division of feeding vessels before interruption of draining veins, avoidance of entering the nidus), but unique to pediatrics is the small circulating blood volume, so that careful measurement of blood loss and close communication with anesthesia are vital to minimize the likelihood of hypovolemia.
- Following resection of the AVM, the craniotomy is closed and the child is transferred to the angiography suite while still under anesthesia. The operating room and equipment are kept sterile in case there is a need to return for additional resection. High-quality angiography is performed. If residual lesion is identified, the child is brought back to the operating room for further resection, and this protocol is repeated (including angiography to confirm complete excision). If the angiogram reveals complete resection of the AVM, the child is awakened and brought to the ICU for recovery.
- Postsurgical management
 - After surgery, the child is managed in the ICU with an arterial line, IV fluids, and a bladder catheter. The child is awake, and a neurologic evaluation is performed every 1 to 2 hours. The blood pressure is liberalized to 10 to 20 mm Hg above the norms for age, although efforts are made to keep the child normotensive. Pain management is often critical to achieving this goal. Diet is advanced as tolerated. No imaging is obtained unless there are specific concerns.
 - Following discharge, children are brought back for follow-up at 4 to 6 weeks. An angiogram is obtained at 1 year postoperatively, and if the angiogram does not show evidence of residual or recurrent AVM, then the child is seen annually with MR imaging and MR angiography for 5 years.

67.8 Operative Technique

Given the wide variety of AVM sizes and locations, it is impossible to identify any single approach for AVM surgery. Specific approaches should be selected to maximize access to the lesion, avoid eloquent neurologic cortex (if possible), and afford the surgeon visualization of feeding and draining vessels to permit proximal control of blood flow.

67.8.1 General Principles

The operating room should be notified to prepare for surgery. It is generally helpful to call to the room (or to the operating room desk the day prior, if possible) to review positioning, medications, nurse staffing, and equipment needs. Equipment should include the operating microscope, multiple suctions, bipolar electrocautery, an array of AVM/aneurysm clips, a craniotome (drill), and a retraction system. Anesthesia should be consulted and appropriate measures taken to ensure that multiple large-bore IV lines are available and that adequate blood products are

in the room. It is helpful to have the microscope draped and clips selected and loaded before the case is started, if possible, so that quick access can be obtained should unexpected bleeding occur during opening.

67.8.2 Craniotomy

Adequate exposure is critical to AVM surgery. It is important not to make the craniotomy too small in order to visualize the lesion safely. The use of frameless stereotaxy and other intraoperative navigation adjuncts (such as ultrasound) can help to minimize risk in these operations. At the time of bone flap removal, it is important to try to avoid tears in the dura so as not to injure subjacent AVM vessels. When opening the dura, be cognizant of potential adhesions between the dura and vessels (► Fig. 67.4). In some cases, it can be helpful to leave dural remnants adherent to the lesion in place and cut around them to avoid tearing surface vessels.

It is common to encounter a tight brain upon opening the dura. Key maneuvers, such as elevating the head of the bed, mild hyperventilation, or the use of osmotic diuretics, may help resolve this problem. Draining the cerebrospinal fluid can be useful, but it is important not to tear vessels while doing so.

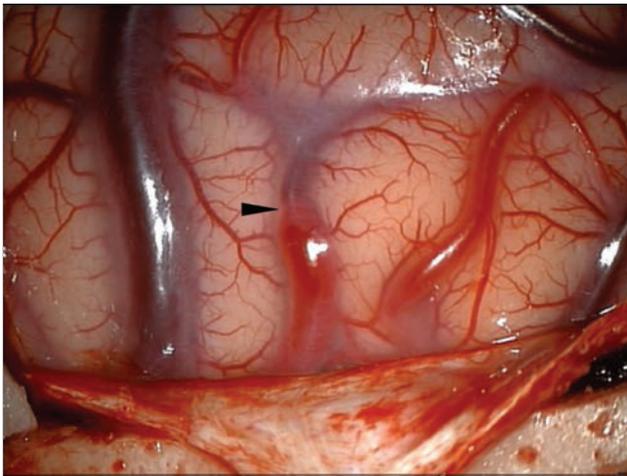


Fig. 67.4 Intraoperative cues for arteriovenous malformation (AVM) localization. Image of cortical surface as seen at the opening for an intraparenchymal AVM. Although the AVM is deep and not immediately visible on opening, an arterIALIZED vein (black arrowhead) gives warning of the lesion below and must be preserved during the initial dissection.

Once the dura is open, several general principles can be applied to nearly all AVM operations. These include:

- A primary surgical principle for AVM resection is the obliteration of feeding arteries before the occlusion of draining veins because premature closure of outflow can lead to unexpected AVM rupture with uncontrolled bleeding.
- AVMs are often wedge- or cone-shaped, and resection can be performed in a circumferential pattern, staying close to—but not entering—the nidus. It is helpful to try to maintain an even depth of resection around the lesion to avoid getting into a “hole,” and caution must be taken to minimize retraction on draining vessels during dissection (► Fig. 67.1, ► Fig. 67.5).
- Repeated inspection of the surrounding brain for swelling or bleeding can reduce complications by allowing the early identification of poorly placed retractors or clips.
- AVM vessels may coagulate poorly, and consideration should be given to clip application or gentle tamponade (if the bleeding is of small volume) if bipolar electrocautery is not working. Every attempt should be made to avoid operating within the nidus itself.

67.8.3 Closure

Inspection of the operative cavity for residual nidus is important, and perioperative angiography can be a useful adjunct to ensure complete resection. Evidence of brain swelling at closure may indicate occult bleeding, untreated hydrocephalus, or poorly compensated redistribution of blood flow, which can result in perfusion breakthrough hemorrhage. Causes of swelling should be thoroughly investigated and treated, if possible, before the patient leaves the operating room. The temporalis muscle and galea are closed with interrupted resorbable sutures, and the skin is closed with a running resorbable suture.

67.9 Postoperative Care

Postsurgical therapeutic maneuvers depend on the presentation. For a healthy child or a child who presents with chronic symptoms (seizure, developmental delay), often no immediate interventions are necessary (with the exception of antiepileptic medication if seizures are present). It is important to note that presentations can vary greatly in severity, and thus treatment has to be individually tailored. It is critical to discuss the management strategy for a patient after surgery with the ICU team

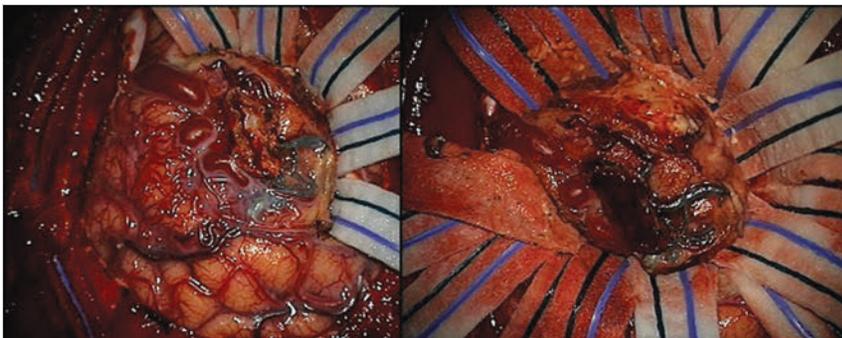


Fig. 67.5 Intraoperative images of a superficial cortical arteriovenous malformation (AVM). Initial image shows dilated draining veins (left). Subsequent image illustrates method of circumferential dissection around the AVM with preservation of the draining vein until the final portion of the case (right). Note the reduction in the caliber of the draining vein and the change to stagnant, deoxygenated venous blood after interruption of the arterial supply.

so that all members of the staff involved with the patient deliver consistent care.

► **Key points include:**

- Blood pressure should be controlled (labetalol or nifedipine) with the goal of normotension for age. However, in some cases with large or high-flow AVMs, a slightly lower than normal blood pressure may merit consideration to minimize the risk for perfusion pressure breakthrough hemorrhage in the immediate (24 to 48 hours) postoperative period.
- Control of the intracranial pressure with placement of an external ventricular drain and elevation of the head of the bed are warranted for a patient with hydrocephalus from hemorrhage.
- Antiepileptic medication should be given if there is concern for seizure.
- Steroids often are not needed (unless they are used as antiemetics).
- Frequent neurologic assessment with examination is important to detect changes that may warrant an imaging study to look for hemorrhage or stroke.

67.10 Treatment Alternatives

67.10.1 Radiation Therapy

Conventional fractionated radiation is not helpful in the majority of AVMs; however, stereotactic radiosurgery offers cure rates of up to 90% in lesions under 3 cm in size. This approach is beneficial for surgically inaccessible lesions or in patients who are high-risk surgical candidates. Shortcomings of this approach include a delay of up to 3 years for lesion obliteration (with unclear data on the changes in hemorrhage risk during this period) and exposure to radiation in children. Radiation has increased risk in younger populations, making its application less appealing in children less than 3 years of age.

Complications

The long delay between treatment and lesion obliteration in radiosurgery for AVMs means that the child is at risk for bleeding during this interval. Patients with small (<3 cm diameter), deep-seated lesions (in the basal ganglia, internal capsule, and thalamus) are the best candidates for radiosurgery. A study of 42 children with lesions in these locations documented a 62% angiographic cure rate within 2 years.⁷⁰ However, radiosurgery in these sites has shown a higher risk of rebleeding when compared to AVMs treated in other areas of the brain.⁷¹

Young children have risk of radiation-induced damage, including injury to the surrounding developing brain and potential for development of secondary malignancies. These risks limit radiation use to older children in most cases whenever possible.

67.10.2 Embolization

Although not traditionally used as a stand-alone treatment for AVMs other than in rare cases with a small nidus and a small number of feeding pedicles, there is a growing literature on the

use of newer embolization agents (Onyx) for definitive treatment of brain AVM in adults. However, the situation in children is more complex and embolization is rarely used as a stand-alone modality, as the recurrence rate is higher, and lesion immaturity may preclude complete visualization angiographically. Regardless, embolization is a significant aid in the treatment of AVMs, reducing their blood supply and facilitating operative approaches (usually <72 hours before surgery). Embolization also has a role in targeted treatment of non-operative lesions, by occluding areas at risk of hemorrhage, such as aneurysms or high-risk varices (those that are intraventricular).

67.11 Outcomes

67.11.1 Outcome after Surgery

Good recovery was achieved in 90% of pediatric patients with Spetzler-Martin grades 1 through 3 AVMs treated by resection,⁴⁹ and deaths occurred at a rate of 5%. Radiographic obliteration rate was 89%. Although level 1 or 2 data are lacking, the combined level 3 data strongly support resection as a primary treatment for patients with Spetzler-Martin grade 1 or 2 AVMs. The relatively low postoperative morbidity rates in patients with these lesions (ranging from 0 to 12%), along with a high rate of complete obliteration (up to 100%), suggests that delayed control, inherent to radiosurgery, may not be warranted.^{24,47,49,55}

67.11.2 Outcome after Nonsurgical Treatments

For comparison, a similar group of patients treated with radiosurgery alone had a reported 80% efficacy rate of lesion obliteration at 36 months, with 4 of 53 patients having recurrent hemorrhage after treatment.⁵⁶ One large pediatric AVM study included 40 patients and confirmed radiographic obliteration of the AVM nidus in 35% of the patients.⁷² The cumulative hemorrhage rate after treatment was 3.2% per patient per year in the first year and 4.3% per patient per year over the first 3 years.⁷² These rates of obliteration, which are notably lower than those reported in the adult population, were potentially complicated by the slightly larger than average size of the treated AVMs in the study group. In contrast, when 53 pediatric patients were stratified by AVM size (<3 cm³, 3 to 10 cm³, and >10 cm³), obliteration rates of 80% and 64.7%, respectively, were reported in the groups with the smallest and medium-size AVMs.⁵⁶

Although level 1 and level 2 data are lacking, the aggregate level 3 data strongly support the use of radiosurgery in the treatment of small (diameter <3 cm), deep-seated lesions in eloquent cortex. For Spetzler-Martin grade 1 and most grade 2 lesions, open resection is generally recommended rather than radiosurgery unless there are specific considerations that make resection unsuitable for the patient. Radiosurgery should be used only for larger lesions (grades 2 through 5) if the objective is complete obliteration of the AVM.³³

67.12 Complications

Bleeding is the most immediate complication of surgery, and risks are magnified in smaller children, who have little reserve.

The loss of one-quarter of the blood volume can induce shock, and there may be rapid decompensation in children, so that careful monitoring and replacement of blood products by the operative team are mandated.

Normal perfusion pressure breakthrough is a phenomenon that is thought to occur after the resection of high-flow AVMs; once the AVM has been removed, blood previously transmitted through the AVM is redirected to smaller, normal vasculature, with the subsequent inability of these vessels to handle the increased flow. This can result in brain swelling, increased intracranial pressure, seizure, neurologic dysfunction, or hemorrhage. The problem may be minimized by staged preoperative embolization and rigorous blood pressure control postoperatively.

Inadvertent occlusion of a normal cerebral artery can occur after embolization or after surgery. In this situation, the blood pressure should be increased temporarily in order to improve collateral supply to the ischemic region.⁷³ This maneuver does not appear to be associated with an increased risk for rupture of the AVM.³³

Neurologic deficit can occur following AVM resection, although specific rates are hard to derive, given the wide variability in AVM size and location.

Overall, postoperative morbidity rates in patients with low-grade (grades 1 through 3) Spetzler-Martin lesions are low (ranging from 0 to 12%) and rates of complete obliteration are high (up to 100%), suggesting that surgical resection of these lesions is warranted, especially when it is performed in experienced centers.^{24,47,49,55}

67.13 Follow-up

Recurrence of an AVM, particularly in the pediatric population, after angiographically confirmed obliteration, including the development of a lesion on the side opposite to the initial AVM, has been reported.^{16,24,47,74–77} AVMs in children may be physiologically different from those in adults, as suggested by their ability to expand and recur, which is possibly related to their expression of angiogenic proteins, such as vascular endothelial growth factor.⁷⁸ Therefore, careful follow-up of these patients is warranted, even after a normal postoperative angiogram. Although the timing of follow-up studies varies by practice, it is the policy in our institution to obtain MR images/MR angiograms at 6 months and an angiogram at 1 year.

67.13.1 Frequency of Office Visits

Postoperative care will frequently consist of an office visit approximately 1 month postoperatively, then annually thereafter. Radiation therapy also involves annual visits after treatment.

67.13.2 Frequency of Imaging

In addition to the perioperative angiogram to confirm obliteration of the AVM, MR images/MR angiograms at 6 months may be helpful as a baseline study, to then be used for comparison with subsequent annual MR images/MR angiograms. Imaging is performed annually for 5 years, if feasible. Digital subtraction

angiography is often performed at 1 year postoperatively to confirm durable cure.⁷⁹

67.13.3 Arteriovenous Malformations and Pregnancy

The treatment of a known AVM should be undertaken before pregnancy whenever possible. There are rare situations of a documented intracranial AVM in a pregnant woman. Either the AVM was not addressed before pregnancy or neurologic sequelae led to its discovery. Data in this small group of patients are inconclusive, particularly with regard to the rate of hemorrhage during the pregnancy.^{74,80–85} MR imaging is safe for initial evaluation of the anatomy of the lesion.⁸⁶ No specific recommendations can be made if the AVM is diagnosed during pregnancy because individual risk-to-benefit relationships need to be assessed. If the mother has an untreated or partially treated AVM, cesarean section should be considered.^{1,40,74,84,87}

Pearls

- The most important surgical decision is whether to operate or not. Whenever faced with an AVM, carefully weigh the risks and benefits of treatment—ideally in a multidisciplinary setting at an experienced center—before embarking on a course of action.
- Maximize the odds for success by formulating a detailed surgical plan. Obtain all imaging needed and review the relevant anatomical landmarks and angioarchitecture before going to the operating room. Understand the potentially risky areas of the resection and plan for possible emergencies.
- Engage your team. Use all resources at your disposal, including embolization, navigation, and the proper surgical tools. Most importantly, talk to your team—anaesthesia, nursing, and ICU staff—so that everyone is prepared for the case before, during, and after.
- During the operation, work from feeders to draining veins. Avoid entering the lesion, and try to tamponade bleeding instead of diving into the nidus. Maintain good lines of sight throughout the case, and frequently change views so as to avoid getting lost or overexposed in a deep hole. Move deliberately and with a plan at all times. Reinspect the brain routinely to make sure there is no unexpected bleeding or swelling out of your field of view.
- At the conclusion of the case, carefully inspect the cavity for residual lesion and consider angiography to confirm resection.

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68 Radiosurgical Management of Cerebrovascular Malformations in Children

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Arteriovenous malformations (AVMs) of the brain are a common cause of hemorrhagic stroke in the pediatric population. In contrast to adults, in whom AVMs cause hemorrhage, seizures, headaches, and progressive neurologic deficits, the majority of children have an initial brain hemorrhage.^{1,2} Because of this risk for hemorrhage and its attendant morbidity and mortality, as well as the lifelong risks of an AVM should it go untreated, the majority of children with brain AVMs undergo some form of therapy. Rather than conservative management, treatment can include microsurgical resection, embolization, or stereotactic radiosurgery, alone or in combination.

Although they are considered to be congenital, it is unclear when brain AVMs actually develop.³ They are thought to develop in the fetus, but the rarity of presentation during the neonatal period has prompted some investigators to question whether AVM development only begins in utero, then progresses during the first years of life.⁴ This possibility also has been raised by various authors, who have noted the recurrence of childhood AVMs despite total resection confirmed by angiography.⁴⁻⁶ Others have noted the association between vascular malformations and tumors.⁷ Some are associated with aneurysms, venous sinus anomalies, or fistulas.⁸⁻¹³ Certainly some AVMs are detected shortly after birth, such as large parenchymal or vein of Galen malformations that present with congestive heart failure.¹⁴⁻¹⁶ Most AVMs are detected between the ages of 20 and 40 years, which may suggest latency in the evolution of the malformation. Perhaps some do evolve in their angioarchitecture, eventually posing a greater and greater risk for the patient.⁶ Nevertheless, 20% of AVMs entered into the first cooperative AVM study were diagnosed before the age of 20 years, and thus the childhood presentation of an AVM is not uncommon.¹⁷ In general, AVMs cause a significant proportion of pediatric strokes and are three times more likely than saccular aneurysms to cause intracerebral hemorrhage in persons younger than 18 years.²

68.1 The Natural History of Arteriovenous Malformations in Children

Matson declared that AVMs were the “most frequent abnormality of the intracranial circulation in childhood.”¹⁸ Because most children with AVMs undergo treatment, reports of untreated patients are too few in number for the natural history of untreated pediatric AVMs to be fully understood. In retrospective series, most authors found a hemorrhage rate at presentation higher than that reported for adults, usually in the range of 80%.^{19,20} In the 40-year Toronto experience published in 1992, Kondziolka et al reported on 132 children. Of these, 27 were managed conservatively, and death followed catastrophic hemorrhage in 13 of them. Of eight evaluable conservatively managed children, six were

normal, one had a seizure disorder, and one had a persistent neurologic deficit.⁶

In the entire Toronto series, the mortality rate from AVM hemorrhage was 25%. This high rate may have been related to a higher incidence of posterior fossa AVMs, in which the initial hemorrhage was often lethal. In the general referral population of the Toronto series, 31 children (24%) had a posterior fossa AVM, a feature that varied significantly from the cooperative study (32 of 453; $p < 0.0001$). At present, there is no evidence that AVMs in younger patients are more likely to lead to severe hemorrhage. It is likely that the pediatric mortality from hemorrhage is related to the higher percentage of AVMs with a deep brain location in children. Fufts and Kelly reported mortality in four of six patients who had posterior fossa AVM hemorrhages.^{21,22}

Ondra et al reported a 24-year AVM follow-up assessment in a Finnish population. They reported an annual hemorrhage rate of 4% (for patients with any presentation) and found no difference in hemorrhage rates related to patient age.²³ Pollock and colleagues performed a comprehensive analysis of AVM natural history hemorrhage risk.²⁴ In this study of angiographic and anatomical AVM criteria, the factors of a prior history of bleeding, a single draining vein, and diffuse AVM morphology were found to be significantly related to risk for hemorrhage. Based on these data, an individual patient with an AVM had an annual hemorrhage rate between 0.99 and 8.9%.²⁴ Although in that study age was not a significant variable, Mori et al reported a higher mortality from AVM-related hemorrhage in children than in adults.²⁵

Although these hemorrhage rates can be used in a discussion with patients or parents regarding brain AVMs, the actual use of such numbers to predict a risk over time is problematic. A simple risk prediction formula for natural history data that maintains each year of risk as independent can be used.²⁶ This formula is as follows:

$$\text{risk for hemorrhage} = [1 - (\text{chance of no hemorrhage})]^{\text{expected years of remaining life}}$$

Thus, for a 15-year-old patient with a 3% annual AVM hemorrhage risk and an expected 62 years of life remaining (according to insurance tables),

$$\text{risk for hemorrhage} = (1 - 0.97)^{62} = 85\%.^{27}$$

Although this formula assumes population homogeneity and a uniform natural history among persons of different ages, it is simple and useful for helping patients and parents understand the lifelong risks associated with untreated AVMs (► Table 68.1).²⁶

It is important to remember that conservative management is rarely advocated for children with brain AVMs. Gerosa et al warned that the poor results (18 of 56 cases) after conservative management in their series indicated that AVMs should be treated, regardless of the mode of presentation.²⁰ Itoyama et al in their natural history study found better outcomes in children younger than 15 years, emphasizing the great capacity of the

Table 68.1 Lifetime risk for arteriovenous malformation hemorrhage

Age at initial presentation (y)	Estimated years to live ^a	Lifetime risk for hemorrhage (%) (2%/y)	Lifetime risk for hemorrhage (%) (4%/y)
0	76	79	96
5	71	76	95
10	66	73	93
15	62	71	92
20	57	68	90

^aEstimates according to 1992 preliminary life tables prepared by the Metropolitan Life Insurance Company (MetLife), New York City.

pediatric brain to recover from stroke.²⁸ In general, the lifelong risk for hemorrhage mandates therapy in most children because the benefits of AVM removal or obliteration outweigh the therapeutic risks entailed. Although some children may wait for several years until they reach an age more suitable for treatment (e.g., we would rarely perform radiosurgery on a child younger than 2 years), observation usually is recommended only when a multimodality approach would have little chance to provide complete obliteration or improvement of neurologic function.

When AVMs are large (Spetzler-Martin grade 5), embolization, radiosurgery, or microsurgery alone, or a combination of these techniques, is not likely to cure significant numbers of patients; it is therefore reasonable to consider conservative management for these children. This is not to say that a large AVM cannot be cured, but the patient must carefully understand the risks involved in this stepwise approach before embarking on a program that may not provide great benefit. We have explored staged-volume radiosurgery for symptomatic patients who have large, critically located AVMs. With this approach, different anatomical components of the AVM are irradiated at 3- to 6-month intervals so that each component receives a high dose; however, the risks can be lessened by reducing regional irradiation and allowing repair of the sublethal effects of radiation.

Factors like location in the brain, arterial supply, suitability for embolization leading to volume reduction, lack of relationship of the AVM with critical functional brain, and well-defined nidus must all be understood as well as possible before treatment is selected. Nevertheless, it is often not possible to know what embolization can accomplish without placement of a catheter and a superselective angiographic assessment. Similarly, it is difficult to know how the brain may respond to surgical resection in individual patients. These variables are complex for patients with large AVMs. Although our understanding of the potential risks of these different treatments has improved, dilemmas remain for both patients and physicians in the choice of specific therapies.

68.2 Stereotactic Radiosurgery

In the late 1980s, stereotactic radiosurgery became an important therapeutic option for children with brain AVMs.²⁹ Radiosurgery is the single-session delivery of a focused volume of radiation to a defined intracranial target. This surgical option has significantly expanded our options in individual patients.

Table 68.2 Brain location of pediatric arteriovenous malformations treated with radiosurgery at the University of Pittsburgh

Brain location	Number	Percentage (%)
Frontal lobe	21	16
Parietal lobe	14	10
Temporal lobe	20	15
Occipital lobe	19	14
Corpus callosum	5	4
Thalamus	22	16
Basal ganglia	16	12
Pineal region	1	0.7
Cerebellum	5	4
Brainstem	14	14

Table 68.3 Spetzler-Martin grade of pediatric arteriovenous malformations treated with radiosurgery

Spetzler-Martin grade	Number	Percentage (%)
1	3	2.2
2	34	25.2
3	58	43.0
4	17	12.6
5	3	2.1
6	23	17.0

Before stereotactic radiosurgery, the options were surgical resection, embolization, and conservative management.²⁷ Many patients continued to have a patent AVM and a risk for hemorrhage. Radiosurgery provided a new therapeutic approach for the management of deeply located malformations in high-risk locations.^{30–34} The increased number of radiosurgical facilities worldwide has been followed by increased use of this technology for pediatric AVMs. During a 17-year interval, we performed Gamma Knife radiosurgery in 159 children with brain AVMs: 85 boys and 74 girls with a mean age of 12 years (range, 2 to 17 years). Indications for radiosurgery included all types of clinical presentation, any brain location, and an AVM diameter of less than 3.5 cm (► Table 68.2). Some families chose radiosurgery over resection for “operable” AVMs in their desire to avoid craniotomy. Most of these children had small AVMs with a nidus that might have been difficult to locate during surgery (► Table 68.3).

68.2.1 Technique

Most children younger than 13 years receive general anesthesia for radiosurgery. Older children usually require light intravenous sedation. Before radiosurgery, patients and parents speak to the neurosurgeon, radiation oncologist, and radiosurgical nurse regarding the procedure and watch a teaching video tape. Children typically tolerate skull frame fixation well. We use the

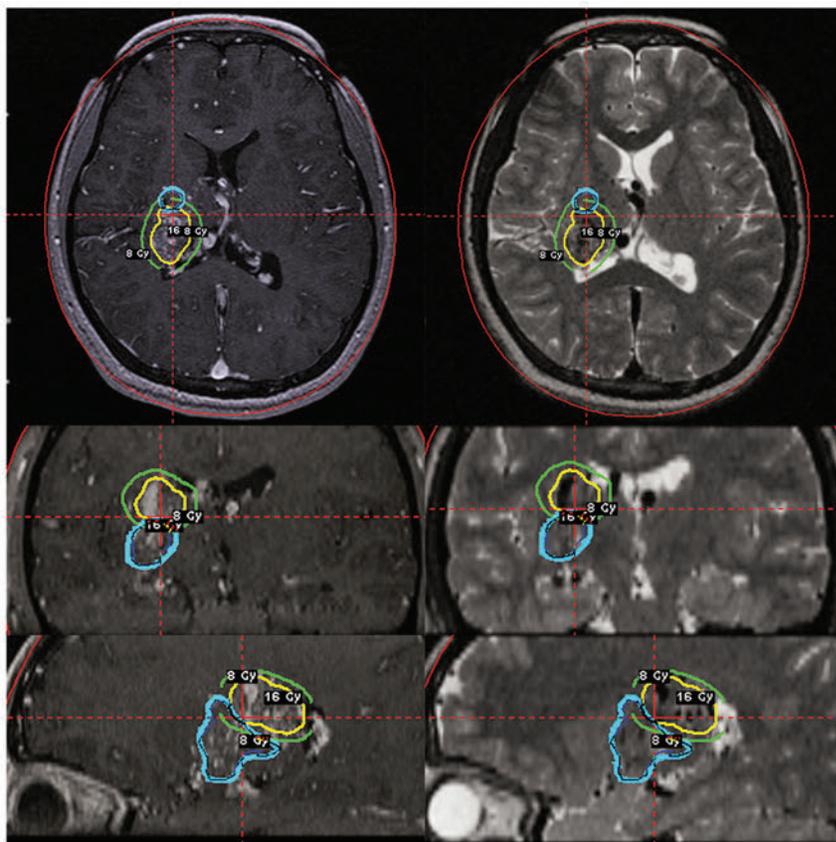


Fig. 68.1 Volume-staged gamma knife radiosurgery plan (16 Gy to the 50% isodose line) for a 12-year-old girl with a thalamic arteriovenous malformation. Axial (upper), coronal (middle), and sagittal (lower) T1-weighted contrast-enhanced and T2-weighted magnetic resonance images showing an anatomical component of the first (blue line) and the second (yellow) volume-staged stereotactic radiosurgery.

Leksell model G stereotactic frame (Elekta, Atlanta, GA), which is applied to the outer table of the skull with four-point fixation. The frame is shifted toward the side of the malformation in an attempt to bring the AVM close to the center of the stereotactic space. Patients then undergo contrast-enhanced stereotactic magnetic resonance (MR) imaging with both short TR (time to repetition) imaging and volume acquisition SPGR (spoiled gradient recalled) sequences, used for MR angiographic reconstruction.³⁵ The majority then undergo stereotactic angiography, with all images transferred digitally to a high-speed computer workstation (► Fig. 68.1 and ► Fig. 68.2).

Radiosurgical dose planning is performed by the neurosurgeon in conjunction with the radiation oncologist and medical physicist. For AVMs with an irregular volume, multiple isocenter plans are created in order to conform the AVM nidus margin to the selected treatment (usually the 50% isodose). The maximal dose is selected based on the weighting of various factors, such as AVM volume, brain location, and pertinent clinical history. With use of the integrated logistic formula (which predicts a 3% risk for permanent radiation-related complications), the appropriate margin dose is selected. We attempt to choose an effective and tolerated dose, balancing the highest obliteration rates achievable with risk factors related to volume and location. Single or multiple isocenter radiation is then performed with the Gamma Knife (Elekta Instrument, Atlanta, GA). As a last step, the stereotactic frame is removed and a local dressing is used to wrap the head. The patient is transferred either to the recovery room (if general anesthesia was required) or back to the hospital room (if local anesthesia was used). All patients are

discharged home the next day. Therapeutic anticonvulsant agents are administered to patients with lobar AVMs. A single intravenous dose of methylprednisolone is administered immediately after radiosurgery.

For follow-up, we obtain MR images at 6- to 12-month intervals after radiosurgery in order to assess both the vascular and the parenchymal response. An angiogram is requested for all patients beginning 3 years after radiosurgery. When complete obliteration or only an early draining vein is identified on the follow-up angiogram, no further treatment is necessary. For patients who have small residual AVM nidus more than 3 to 3.5 years following radiosurgery, additional treatment is usually required to complete the obliteration. This may involve either microsurgical resection or repeated radiosurgery.

68.3 The University of Pittsburgh Experience

In the University of Pittsburgh pediatric series, 87 patients (64%) presented with a hemorrhage, 16 (12%) had headache, and 20 (15%) had experienced prior seizures. Extraocular movement dysfunction was noted in 1 (0.7%) and hand intention tremor in 1 (0.7%). In 10 patients (7%), the diagnosis was made by imaging during the evaluation of a problem unrelated to the AVM. A neurologic deficit was present in 54 patients (40%) at the time of radiosurgery. Prior subtotal surgical resection (range, 1 to 4 operations) had been performed in 22 children (16%). Embolization was performed in 25 patients (19%) in an

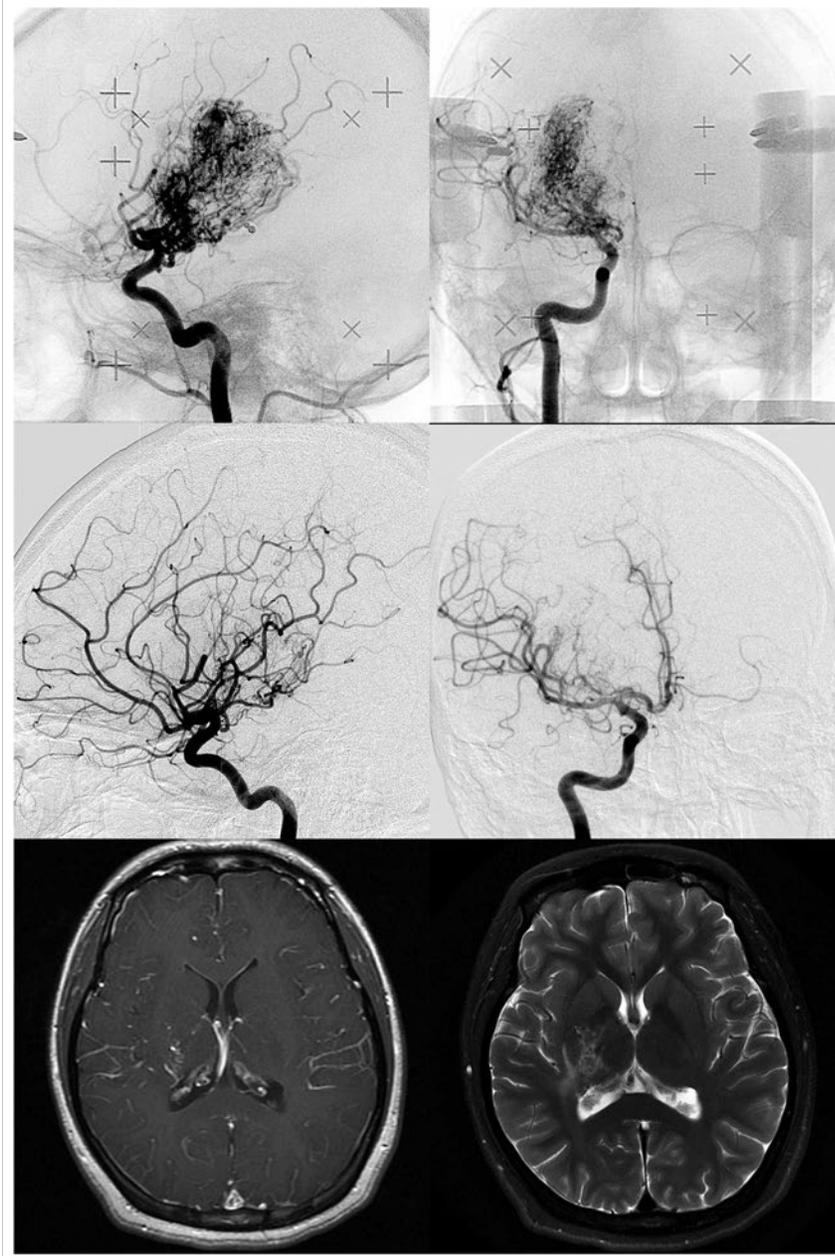


Fig. 68.2 Upper: Angiograms showing a 12-year-old girl with a thalamic arteriovenous malformation at the time of Gamma Knife radiosurgery. Middle: Angiograms showing total obliteration 38 months after a second volume-staged radiosurgery. Lower: Axial T1-weighted contrast-enhanced and T2-weighted magnetic resonance images showing total obliteration with a slight abnormal area on the T2-weighted image.

attempt to reduce the size of the AVM before radiosurgery. The AVMs were located in the cerebral hemispheres in 74 patients, the cerebellum in 5, the corpus callosum in 3, the thalamus in 22, the basal ganglia in 16, the pineal region in 1, and the brainstem in 14. A Spetzler-Martin grade 1 AVM was diagnosed in 3 (2%), grade 2 in 34 (25%), grade 3 in 58 (43%), grade 4 in 17 (13%), grade 5 in 3 (2%), and grade 6 in 23 patients (17%).

The mean AVM volume in this series was 2.5 mL (range, 0.1 to 17.5 mL). The median number of isocenters was 4 (range, 1 to 17). The median dose selected to the AVM margin was 20 Gy (range, 15 to 25 Gy), and the median maximum dose was 40 Gy (range, 30 to 50 Gy). In general, an AVM margin dose of 23 to 25 Gy was delivered if possible. This dose range has been associated with the highest obliteration rate in published studies.³⁶ The selected dose is not specifically lower for children than for adults, but attention is paid to AVMs near the

hypothalamic-pituitary axis before radiosurgery is chosen as a treatment. We limit irradiation of the pituitary region in an attempt to avoid risks for growth delay. The risk for an AVM hemorrhage is neither increased nor decreased by radiosurgery until complete obliteration has occurred.³⁷

68.3.1 Arteriovenous Malformation Obliteration

In our study,³⁸ obliteration rates after radiosurgery documented by either angiography or MR imaging criteria were 45%, 64%, 67%, and 72% at 3, 4, 5, and 10 years, respectively, with a median of 71 months of follow-up. The median time until documentation of total obliteration on MR imaging was 37 months. In 81 patients with 4 years or more of follow-up, 57 patients

(70%) had total obliteration documented by angiography. Factors associated with a higher rate of documentation of AVM obliteration were smaller AVM target volume, smaller maximum diameter, and larger margin dose.

Tanaka et al compared their results after Gamma Knife radiosurgery in 23 children and 76 adults whose mean AVM volumes and margin doses were similar. They found 1-year complete obliteration rates of 74% in children and 45% in adults, and 2-year complete obliteration rates of 95% and 81% in children and adults, respectively.³⁹ These data lend further support to the concept of a higher obliteration rate in children. Pan et al⁴⁰ reported that AVM obliteration was achieved in 48 (65%) of 74 pediatric patients at 4 years after initial stereotactic radiosurgery. Additional stereotactic radiosurgery, when needed, led to an overall total obliteration rate of 81%.

68.3.2 Risk for Hemorrhage after Radiosurgery

In the previous series, the annual hemorrhage rate for pediatric AVMs after stereotactic radiosurgery ranged from 0.56 to 3.2%.^{33,40–45} In our study,³⁸ 8 patients (6%) had a hemorrhage during the latency interval, and 1 patient died. The rates of AVM hemorrhage after stereotactic radiosurgery were 0%, 1.6%, 2.4%, 5.5%, and 10.0% at 1, 2, 3, 5, and 10 years, respectively. The overall annual hemorrhage rate was 1.8%. Larger-volume AVMs were associated with a significantly higher risk for hemorrhage after stereotactic radiosurgery. No patient bled after documentation of AVM obliteration with either MR imaging or angiography. A larger target volume was associated with higher rate of hemorrhage after stereotactic radiosurgery.

68.3.3 Results for Arteriovenous Malformations Causing Seizures

Seizures are the second most common presenting symptom of vascular malformations, occurring in 15 to 20% of cases. For children with seizures related to an AVM, the goal of radiosurgery is both AVM obliteration and cessation of seizures. Gerszten et al reviewed our experience in children younger than 18 years who had radiosurgery for AVMs that caused seizures.⁴⁶ Before radiosurgery, 13 children had seizures; seven had a single seizure and six had multiple seizures. Two children had intractable simple partial seizures. Six patients also had an intraparenchymal hemorrhage. Previous treatments included partial surgical resection (n=3) and embolization (n=7). At 1 year after radiosurgery, 11 of the 13 children (85%) with seizures were seizure-free and required no anticonvulsant therapy. Two of these children had a single generalized tonic-clonic seizure after radiosurgery and were found to have subtherapeutic levels of anticonvulsant medication. Both were later successfully weaned from medication. Two patients had a significant decrease in the frequency and severity of simple partial seizures but did not become seizure-free. No difference was found between seizure outcome in children with complete obliteration of their AVM and that in children with residual AVM at follow-up of at least 1 year.

It is still not known whether complete removal or obliteration of an AVM leads to consistent control of seizures. Also, no relationship has been established between the occurrence of a

preoperative bleed and the likelihood of its causing or aggravating a seizure disorder afterward. In adult radiosurgery series, good seizure control occurs in more than 70% of patients; better results are identified with increasing age and a higher dose of radiation.⁴⁷ Because the neural tissue surrounding the AVM, not the lesion itself, is the epileptogenic focus, the effect of radiosurgery on the surrounding brain may be related to hemodynamic effects, local irradiation, or some other factor. Some effect of radiosurgery on the brain surrounding the AVM, perhaps improvement of regional brain perfusion, may diminish the neuronal epileptogenic potential. Because the outcome of a child with a seizure disorder may be different from that of an adult with seizures, in terms of both social and intellectual development, an attempt to obtain complete control of seizures without medications is warranted in all patients. Whether surgical extirpation, radiosurgery, or embolization is necessary remains to be determined in individual patients. Children with intractable seizures and an AVM might benefit from inclusion in a preoperative epilepsy protocol in which a combination of approaches could further improve seizure outcome. Because radiosurgery is used for both “resectable” and “unresectable” AVMs, comparisons between outcomes after radiosurgery and those after resection are warranted.⁴⁸ Knowledge of the anatomical lesion (AVM) and the functional lesion (epileptic focus) likely is probably necessary to obtain an even higher rate of seizure control.

68.3.4 Morbidity of Radiosurgery

Early complications after radiosurgery are rare. Some children may experience brief nausea after anesthesia. All patients have been discharged from the hospital within 24 hours. An immediate postoperative seizure has been rare in our experience since we instituted a protocol of preoperative anticonvulsant agents in patients with subcortical lobar AVMs.

As AVM obliteration occurs, parenchymal changes can be identified on serial imaging studies that may or may not be symptomatic, depending on location in the brain.⁴⁹ Brainstem AVMs are associated with a higher incidence of complications than supratentorial AVMs.^{50–52}

Long-term results are especially important for children and young adults. In our series,³⁸ eight patients (6%) developed adverse radiation effects after stereotactic radiosurgery at a median of 6.6 months (range, 2.8 to 13.2 months). Permanent neurologic deficits developed in two of six patients. A factor associated with a higher rate of symptomatic adverse radiation effects was an AVM location in the brainstem, thalamus, or basal ganglia. Delayed cyst development was diagnosed in one patient (0.7%) with a prior hemorrhage at 56 months after stereotactic radiosurgery, but no additional treatment was required. Yamamoto et al reported the occurrence of cystic parenchymal changes years after AVM obliteration, and we have seen this in two patients in our series.⁵³ We have not noted a delayed radiation-induced malignancy in our experience of 12,000 patients managed for various disorders.

68.3.5 Role of Embolization before Stereotactic Radiosurgery

Embolization of larger-volume AVMs is sometimes performed before stereotactic radiosurgery in an effort to increase the

probability of complete obliteration.^{21,29,54} The goal of embolization is quite specific when it precedes radiosurgery: permanent volume reduction. Recanalization of a portion of an embolized AVM that lies outside the irradiated volume will place the patient at continued risk for bleeding. Of 45 patients who underwent repeated AVM radiosurgery at our center, 19 (42%) had previously undergone one or more embolization procedures to reduce the volume of the AVM.⁵⁵ Of these 19 patients, 3 (16%) required second-stage radiosurgery because a portion the embolized AVM recanalized after radiosurgery. Recanalization of AVMs has been observed with both acrylates^{56,57} and polyvinyl alcohol.^{58,59} Lasjaunias et al stated that they have not observed recanalization of an AVM at later follow-up when the angiographic findings at 6 to 12 months were strictly normal.⁶⁰ Embolization also has the potential to divide an AVM into multiple compartments, which can make conformal dose planning difficult.^{14,29} Multivariate analysis has shown prior embolization to be a negative predictor of successful AVM radiosurgery.⁶¹ As a result, we are using embolization before radiosurgery less frequently in the management of larger-volume AVMs.

68.4 Cavernous Malformations of the Brain

Cavernous malformations can occur sporadically or as an autosomal-dominant familial disorder. They are composed of endothelial cell-lined sinusoids without intervening brain tissue. Although most cavernous malformations are identified in adult patients with minimal or no symptoms when an imaging study is performed, children who have cerebral cavernous malformations usually are symptomatic. Related symptoms can include brain hemorrhage, seizures, and focal neurologic deficits.⁶² Multiple cavernous malformations usually are seen as part of a familial disorder. In this setting, parents and siblings should undergo imaging studies for both genetic counseling and the identification of specific lesions. It may also be that cavernous malformations develop over time, perhaps first as a microscopic lesion that through repeated microhemorrhage slowly enlarges and subsequently becomes apparent on an imaging study. Mixed cavernous and venous malformations can also occur, with symptoms referable to bleeding or regional venous hypertension.⁶³ Horowitz and Kondziolka identified increasing numbers of malformations within different generations of the same families studied with MR.⁶⁴

Cavernous malformations that are incidentally recognized have a low annual rate of bleeding. In a large prospective natural history study, Kondziolka et al identified a 0.6% annual hemorrhage rate in patients without a prior symptomatic hemorrhage.⁶⁵ This finding occurred regardless of age, brain location, or type of presentation (i.e., seizures or headache). However, in patients who had sustained a prior symptomatic hemorrhage, the subsequent annual hemorrhage rate was a magnitude higher, with a 4.5% annual risk for bleeding.⁶⁵ Thus, children who are found to have a symptomatic cavernous malformation often will require treatment. For those with a single symptomatic lesion, surgical resection should be performed when the malformation is located in a brain region where resection is feasible. If the lesion is contained entirely within the

substance of the thalamus or brainstem, resection may not be appropriate. We have used radiosurgery in both children and adults when prior multiple hemorrhages and a deep brain location mandated treatment.^{66,67} In this setting, radiosurgery was associated with a significant reduction in the hemorrhage rate over time, especially after a 2-year latency interval.⁶⁸ However, the lack of an imaging test that confirms cure and the potential morbidity of radiosurgery in the brainstem or thalamus argue for its use only in symptomatic patients with malformations in critical locations. To date, 12 children with cavernous malformations have had radiosurgery at our center (mean age, 11 years), with a median of 2 symptomatic hemorrhages per patient (range, 1 to 10).⁶⁹ Brain locations included the pons/midbrain (n=6), thalamus,¹⁹ and frontal, parietal, occipital, and temporal lobes (1 in each). The mean radiosurgery margin dose was 15.6 Gy. One patient had 3 symptomatic hemorrhages within 2 years after stereotactic radiosurgery. One patient had 1 symptomatic hemorrhage 2 years after stereotactic radiosurgery. The other 8 patients did not have hemorrhage after stereotactic radiosurgery at a median follow-up of 3 years.

68.5 Venous Malformations (Anomalies)

Venous malformations are congenital anomalies of the venous circulation. Although they are developmental anomalies, they provide drainage of normal brain tissue. Venous malformations usually are located between the deep and superficial venous systems. Common brain locations include the cerebellar hemispheres, brainstem, basal ganglia, frontal lobe, and parietal lobe. Often, venous malformations are diagnosed as an incidental finding on a computed tomographic scan, MR image, or angiogram. There has been no consistent relationship between venous malformations and headaches. Even in patients who present with seizures and are found to have a venous malformation, a causative link is difficult to identify. Some investigators have found that the epileptogenic focus identified by electroencephalography is anatomically separate from the venous malformation.⁷⁰ Thus, a specific treatment directed at the venous malformation in some patients may not relieve symptoms.

In several natural history studies, venous malformations have been associated with extremely low annual hemorrhage rates.⁷¹ Although they are occasionally associated with hemorrhage (perhaps when they coexist with a cavernous malformation), resection of a venous malformation usually is not warranted. In the setting of a large hemorrhage in a noncritical location, the venous malformation and hematoma can be removed with relatively low risk. The surgeon must remember that resection of the venous malformation will eliminate the venous drainage from that brain region. If the brain region is critical, then a symptomatic venous infarction may occur. For this reason, many surgeons would evacuate only the hematoma and leave the venous malformation intact. Rothfus et al reported the resection of cerebellar venous malformations in children who had sustained hemorrhages.⁷² Adverse outcomes due to brain edema have been reported after the use of radiosurgery for venous malformations.⁷³ In general, these functional venous anomalies should be ignored, although they are of clinical and imaging interest.

Pearls

- For most children older than 12 years, radiosurgery can be performed with intravenous sedation and local anesthesia.
- Endovascular embolization immediately after radiosurgery can be used in selected patients to eliminate specific hemodynamic risk factors, such as aneurysms.
- Repeated or staged radiosurgery procedures may be required to achieve total AVM obliteration with significant reduction of risk for hemorrhage.
- Stereotactic radiosurgery for cavernous malformations and AVMs in cortical locations can be associated with a significant reduction in risk for hemorrhage over time.
- Radiosurgery is not an appropriate therapeutic choice for a patient with a cerebral venous malformation. Such deep venous anomalies should be left alone.

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69 Vein of Galen Aneurysmal Malformation

Alejandro Berenstein and Yasunari Niimi

Vein of Galen aneurysmal malformation (VGAM) is a rare vascular malformation involving the embryonic precursor of the vein of Galen. “Vein of Galen malformations” are reported to account for fewer than 1% of all arteriovenous malformations (AVMs) in the cooperative study of subarachnoid hemorrhage.^{1–3} However, the true incidence is difficult to determine because significant diagnostic confusion exists among the various malformations that involve or drain into the vein of Galen or its embryonic precursor, the median vein of the prosencephalon. We define VGAM as a purely fistulous AVM draining to the median vein of the prosencephalon. Other vascular lesions that cause dilatation of the true vein of Galen are defined as vein of Galen aneurysmal dilatation (VGAD) or vein of Galen varix (VGV). VGADs are a group of malformations that drain pial or dural shunts into the true vein of Galen or its tributary and are associated with dilatation of the vein of Galen. VGV is a dilated vein of Galen without arteriovenous (AV) shunts. We describe the vascular anatomy, types, clinical manifestations, natural history, treatment, and outcome of VGAM and its distinctions from VGAD and VGV.

69.1 Vascular Anatomy

Raybaud et al⁴ reported in 1989 that the dilated midline vein in VGAM is not the true vein of Galen but its embryologic precursor, the median vein of the prosencephalon. Based on analysis of the vascular anatomy of VGAM and vascular embryology, a VGAM likely forms within an embryonic stage of 21 to 23 mm (6 weeks) and 50 mm (11 weeks), during the time when the vein of Galen and straight sinus normally develop from a transient precursor, the median vein of the prosencephalon.⁴

Therefore, a true vein of Galen does not exist in VGAM. Moreover, in VGAM, the median vein of the prosencephalon drains only AV shunts. In VGAM, the normal deep cerebral structures drain through alternate venous pathways, typically through a vein that has an epsilon shape on the lateral view of a cerebral angiogram.^{5,6} Further drainage of the malformation is in most cases through the embryonic falcine sinus (precursor of the straight sinus) to the superior sagittal sinus. A straight sinus is usually absent, and persistence of other embryologic sinuses, such as occipital and marginal sinuses, is frequently observed in patients with VGAMs. Persisting arterial anomalies such as a limbic arterial ring involving the anterior and posterior choroidal arteries and pericallosal arteries are also frequently present.

The AV fistula in VGAM can be single or multiple. Arterial anastomoses between feeding pedicles are often seen. Two subtypes of VGAM, choroidal and mural, can be distinguished.

69.2 Classification

69.2.1 Choroidal Vein of Galen Aneurysmal Malformation

In choroidal VGAM (► Fig. 69.1), multiple fistulas are located in the subarachnoid space in the choroidal fissure. These multiple

fistulas communicate with the anterior aspect of the median vein of the prosencephalon. The arterial feeders are usually bilateral anterior and posterior choroidal arteries, a subforniceal branch, pericallosal arteries, and subependymal branches of thalamoperforators. This type of VGAM usually causes high-output cardiac failure in newborns because of the presence of multiple high-flow fistulas with less outflow restriction than in the other type of VGAM. This type of VGAM can be recognized by its complex arterial network and is the more aggressive manifestation of the disease. These lesions are more challenging to treat because of comorbid severe cardiopulmonary failure.

69.2.2 Mural Vein of Galen Aneurysmal Malformation

In mural VGAM (► Fig. 69.2), the fistula is located in the subarachnoid space in the wall of the dilated median vein of the prosencephalon, usually along its inferolateral margin. The vessels supplying the shunt are usually the collicular and/or the posterior choroidal arteries and may be unilateral or bilateral. In contrast to the choroidal-type VGAM, the mural type has fewer fistulas and typically has more outflow restriction, which leads to dilatation of the median vein of the prosencephalon but may protect against high-output cardiac failure. The mural type of VGAM, therefore, clinically presents later in infancy with macrocephaly or failure to thrive and may be associated with mild cardiac failure or asymptomatic cardiomegaly.

69.2.3 Vein of Galen Aneurysmal Dilatation

In contrast to VGAM, the midline ectatic vein in this group of lesions is the true vein of Galen. The vein of Galen, therefore, receives drainage from normal brain as well as from the malformation. Two types of VGAD, parenchymal and dural, can be distinguished.

Parenchymal Arteriovenous Malformation with Vein of Galen Aneurysmal Dilatation

Parenchymal VGADs (► Fig. 69.3) are subpial brain AVMs that drain into a tributary of the vein of Galen. Aneurysmal dilatation of the vein of the Galen is secondary to an outflow obstruction. Outflow obstruction develops in many pediatric fistulous malformations of the brain. The etiology of this outflow obstruction is unknown but may be related to underdevelopment of the jugular bulb, abnormal skull base maturation, and high-flow angiopathy of the venous system causing kinking or thrombosis at the tentorial or dural edge at the skull base. Because of this outflow restriction, the vein of Galen dilates and blood is refluxed into other, normal cerebral veins (internal cerebral, vermian, hippocampal, basal, medial ventricular, parietal, and occipital veins or other normal tributaries of the vein of Galen).



Fig. 69.1 A male patient presented with severe congestive heart failure (CHF) and acidosis at birth. His Apgar score was 5, with severe respiratory distress. The head circumference was 50 cm and the weight was 3.3 kg at birth. The patient was intubated and placed on dopamine and dobutamine drip as well as on furosemide. (a) A computed tomographic scan at 2 days old demonstrates a dilated midline vessel suggesting a vein of Galen aneurysmal malformation (VGAM) and mild hydrocephalus. Because of progression of the CHF, the patient underwent cerebral angiography and endovascular treatment at 4 days of age. Left vertebral artery injection in (b) anteroposterior (AP) and (c) lateral views demonstrates a choroidal-type VGAM draining to the median vein of the prosencephalon, then to the embryonic falx sinus. Multiple fistulas to the anterior portion of the median vein of the prosencephalon are supplied by bilateral posterior choroidal arteries and thalamoperforators. No straight sinus is seen. (d) After the left vertebral angiogram, the left posterior choroidal feeder was superselectively catheterized. Superselective angiogram shows a high-flow fistula. This was embolized with *N*-butyl-cyanoacrylate (NBCA) under systemic hypotension. (*continued*)

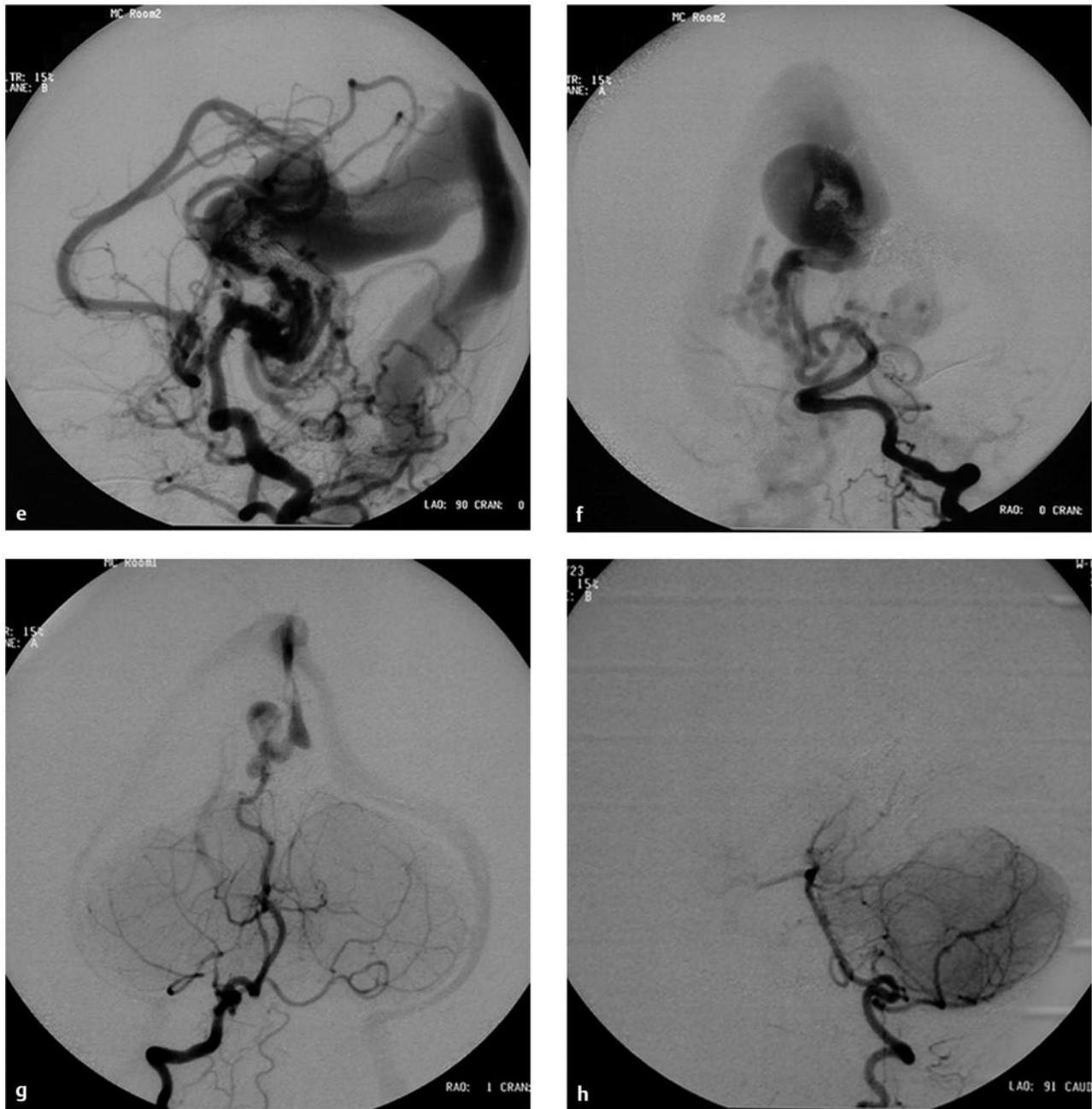


Fig. 69.1 (continued) (e) After embolization of the left common carotid artery, the lateral view demonstrates the remaining fistulas supplied by the posterior choroidal arteries and the left anterior cerebral artery. (f) After embolization of the left vertebral artery, angiogram demonstrates decreased but remaining fistulas. The patient underwent another embolization at 11 days old because of persistent CHF. At 11 months old, the patient underwent a third-stage embolization. At this time, the patient had no CHF but had moderate developmental delay with hypotonia. (g) Right vertebral artery angiogram in the AP view demonstrates a significant decrease in the size of the fistula and the median vein of the prosencephalon. The remaining fistula is supplied by the posterior thalamoperforator, which is increased in size compared with the previous angiogram [compare with (f)]. Complete occlusion of the VGAM was accomplished by the third embolization. (h) The right vertebral artery in the AP view demonstrates no opacification of the remaining fistulas. Distal posterior cerebral arteries are not opacified in this injection. (continued)

This type of VGAD usually presents in childhood or young adulthood with intracerebral hemorrhage, focal neurologic deficit, or seizures. The differentiation between a VGAM and a tectal AVM based only on angiography can sometimes be difficult, but demonstration of transmesence-

phalic feeders by magnetic resonance (MR) imaging confirms a tectal location and VGAD.⁷ For treatment, transvenous embolization is **contraindicated** in VGAD because it may produce extensive venous thrombosis in deep cerebral veins.

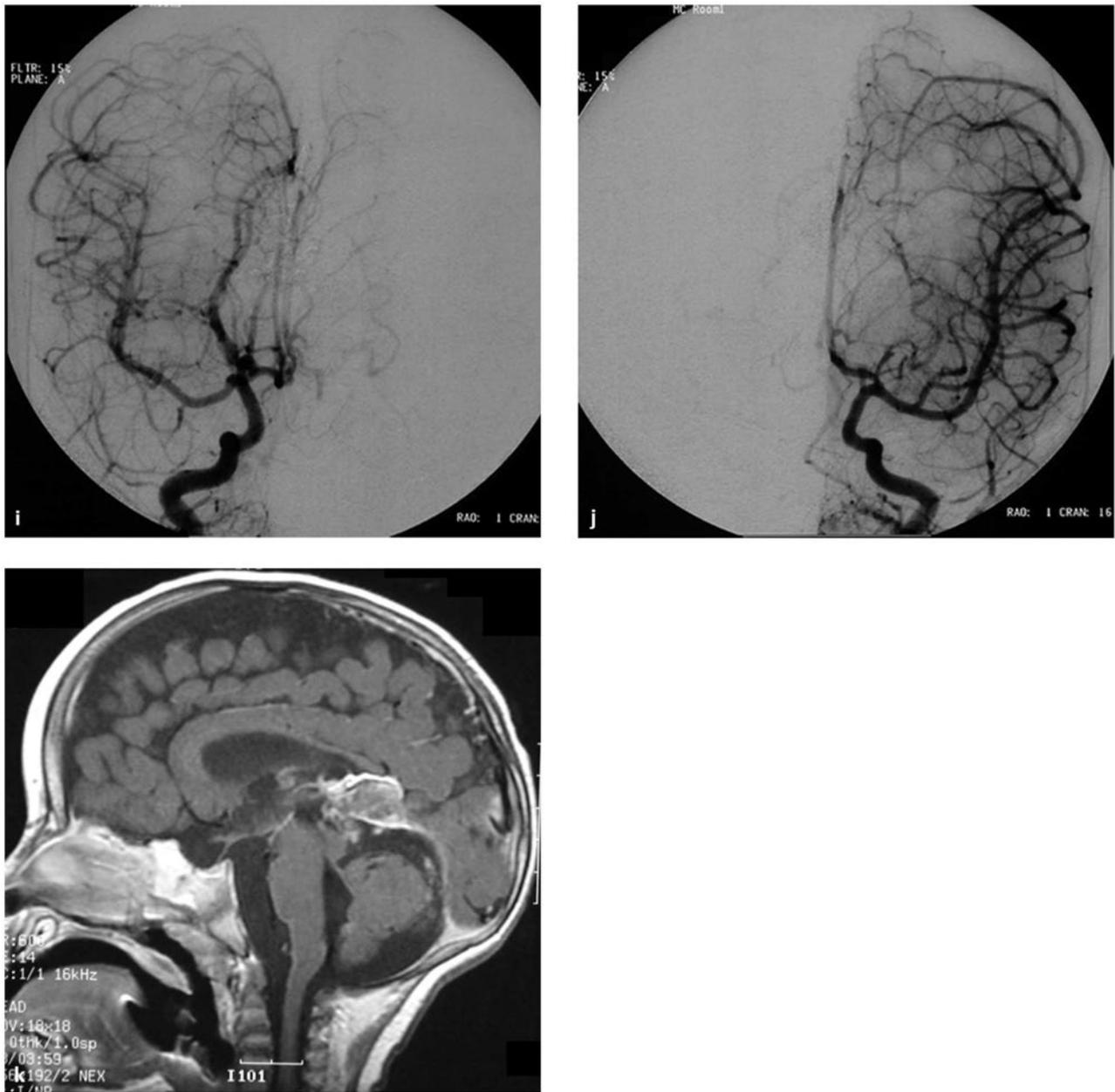


Fig. 69.1 (continued) (i) Right and (j) left common carotid artery angiograms in the AP view demonstrate no opacification of the fistulas. Distal posterior cerebral arteries were opacified through the posterior communicating artery bilaterally. The patient remained with moderate developmental delay. (k) T1-weighted sagittal magnetic resonance imaging with contrast 2 days after the third embolization demonstrates thrombosis and shrinkage of the median vein of the prosencephalon and the embryonic falcine sinus.

Dural Arteriovenous Malformation with Vein of Galen Aneurysmal Dilatation

Dural AVMs with VGAD are acquired lesions, usually presenting in the fourth or fifth decade of life, in which AV shunts are located in the wall of the vein of Galen itself. The dilatation of the vein of Galen is secondary to straight sinus stenosis or thrombosis. Reflux is always noted into afferent cerebral veins from the vein of Galen. The clinical presentation is similar to that of other dural AVMs draining into cerebral veins. Although the number of patients is small, the risk for progressive dementia in

this group is higher than in patients with other dural AVMs. The arterial supply of a dural AVM with VGAD is predominantly from dural falcotentorial arteries of the carotid or vertebral system and from the vasa vasorum to the wall of the vein of Galen, which arise from pial arteries.⁸

69.2.4 Vein of Galen Varix

VGV is dilatation of the vein of Galen without the presence of an AV shunt. Two types have been encountered in children. One is transient dilatation of the vein of Galen in neonates

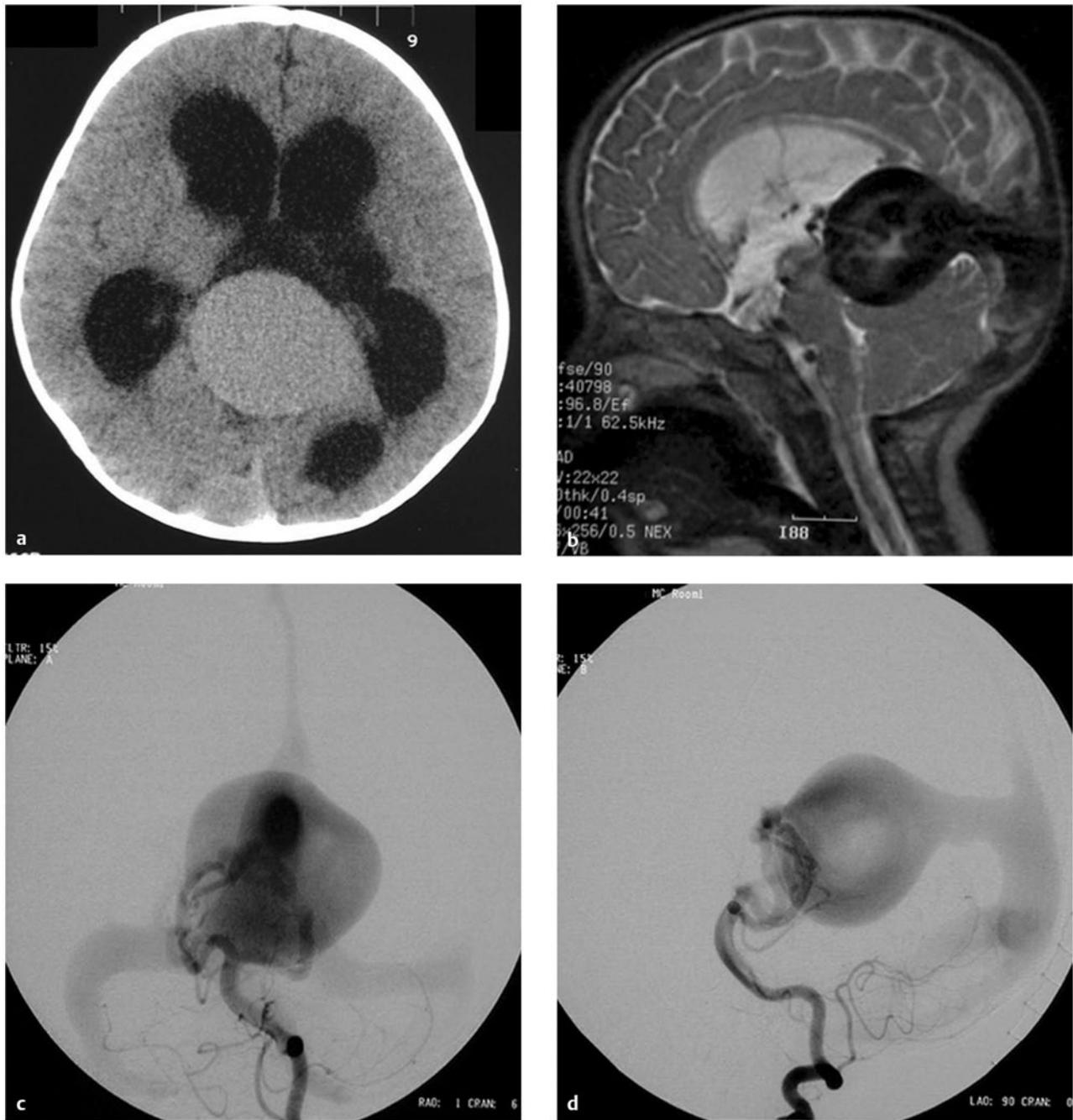


Fig. 69.2 A 6-month-old female patient presented with macrocephaly. The patient was developing normally. (a) Computed tomographic scan without contrast demonstrates hydrocephalus and a large midline vascular structure. (b) T2-weighted sagittal magnetic resonance (MR) image demonstrates a large midline vein draining to the embryonic falx and hydrocephalus. Left vertebral artery in the (c) anteroposterior (AP) and (d) lateral views demonstrates a mural-type vein of Galen aneurysmal malformation (VGAM) supplied by bilateral posterior choroidal arteries. The dilated median vein of the prosencephalon is draining to the embryonic falx with reflux to the superior sagittal sinus. (*continued*)

presenting with cardiac failure from a cause other than VGAM. This dilatation is usually noticed on an ultrasound study and disappears in several days following improvement of cardiac conditions. The dilatation itself does not cause symptoms. The second type of VGV occurs as an anatomical variation in which venous drainage of the brain converges toward the deep venous system. It is asymptomatic, but the lack of compliance of this

type of venous drainage may predispose to future venous thrombosis and resultant ischemic symptoms.

69.3 Clinical Presentation

Characteristic clinical manifestations of VGAM occur in each age group, neonatal and infant. In neonates, cardiac failure is

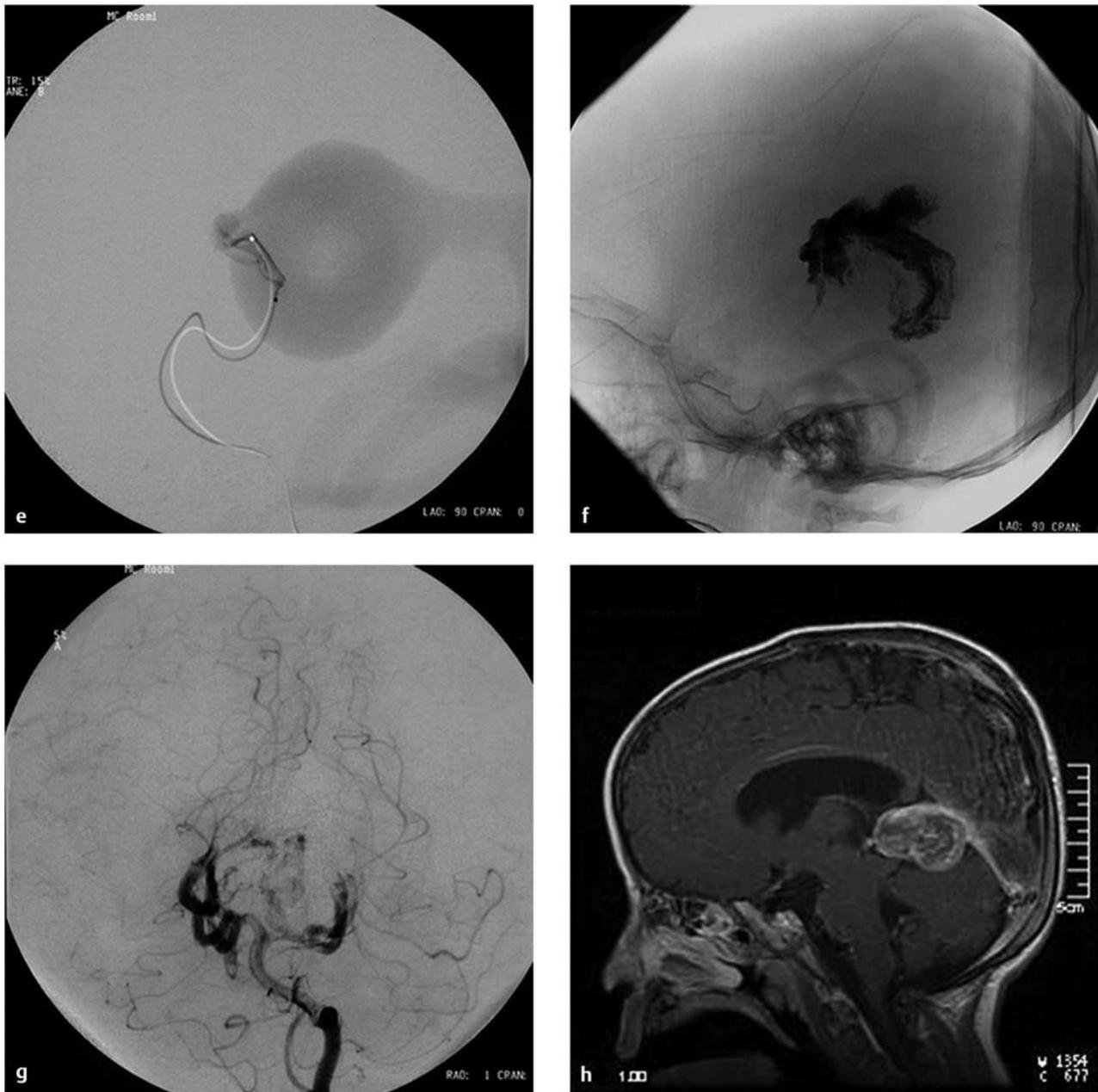


Fig. 69.2 (continued) (e) Superselective angiogram of the left posterior choroidal artery showing a high-flow fistula. This was embolized with *N*-butylcyanoacrylate (NBCA). (f) Lateral skull film showing the NBCA cast penetrating into the venous side. (g) Left vertebral angiogram in the AP view after one NBCA embolization demonstrating almost complete obliteration of the fistulas with minimal residual shunting, showing that this VGAM was a single-hole mural-type fistula. (h) T1-weighted sagittal MR image with contrast 5 months after the embolization demonstrating complete thrombosis and shrinkage of the dilated vein. The ventricular size also decreased without ventriculoperitoneal shunt. The patient remained neurologically normal with normal development.

usually the most prominent clinical feature, whereas in infants hydrodynamic macrocephaly and neurologic symptoms are more frequent.

69.3.1 Neonatal Cardiac Failure

In the neonate, cardiac failure is the most pressing symptom, ranging from asymptomatic cardiomegaly to multiple-organ failure. The reasons for this wide spectrum of cardiac manifestations

are still poorly understood. The size of the shunt, the type of venous drainage, the degree of outflow restriction, the complexity of the arterial supply to the VGAM, and the different responses of individual patients to cardiac stress are contributory. After a brief initial period of stabilization, in most cases the neonate's congestive heart failure (CHF) worsens during the first 3 to 5 days of life, then stabilizes and improves with appropriate medical management. Severe heart failure can cause neurologic dysfunction in newborns with VGAM. Cyanosis can be associated

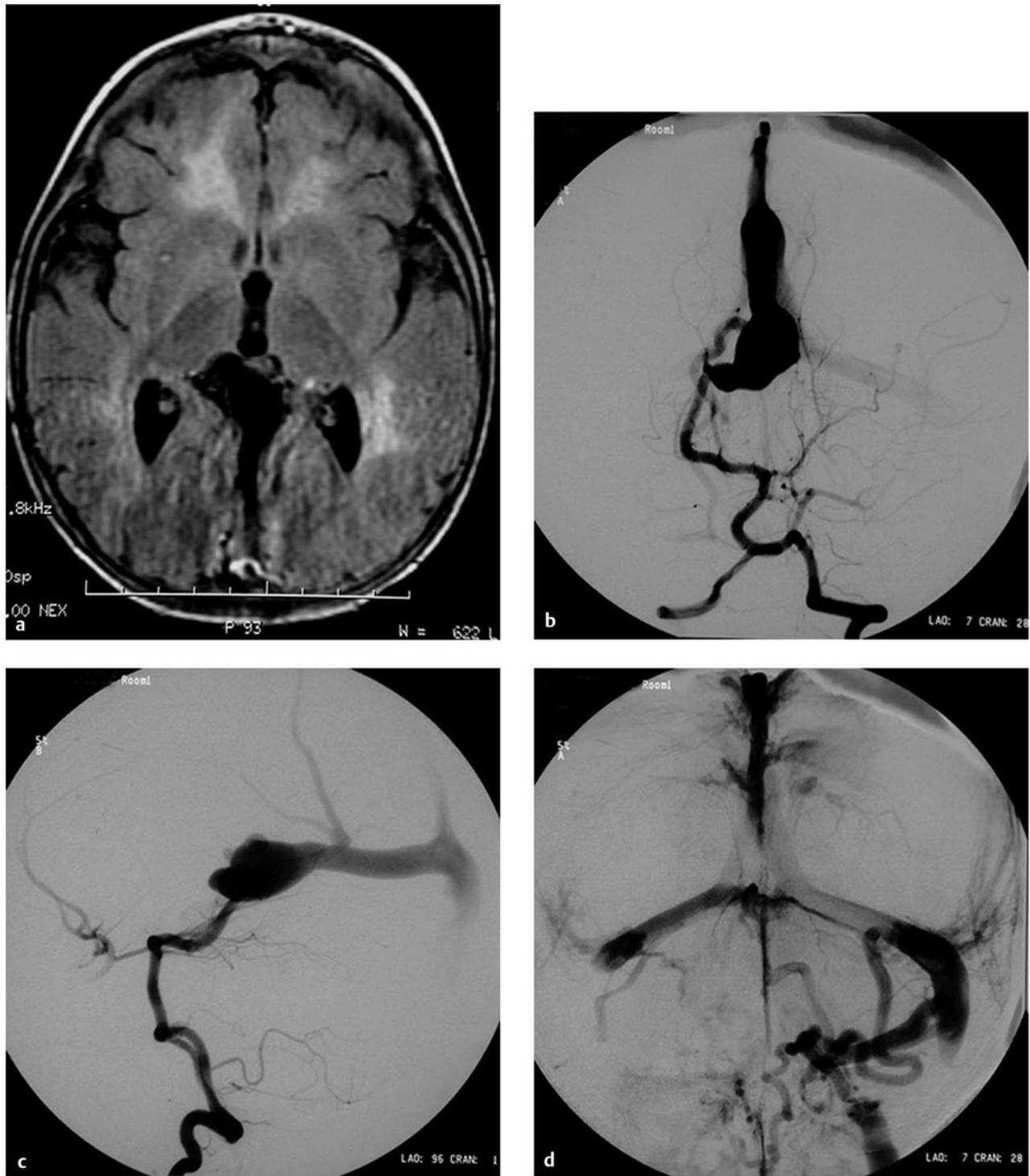


Fig. 69.3 A 12-month-old male patient presented with a 1-month history of seizures. (a) Magnetic resonance (MR) image demonstrates evidence of diffuse brain congestion and midline vascular malformation. The night before the angiography, the patient became obtunded with opisthotonic posturing. (b) Frontal and (c) lateral angiograms demonstrate an arteriovenous fistula from the right posterior choroidal artery to the dilated vein of Galen, which drains to the embryonic falcine sinus. There is reflux of venous drainage to the right basal vein of Rosenthal and the superior and inferior sagittal sinuses. (d) Late venous phase demonstrates significant venous stagnation and occlusion of both sigmoid sinuses with suboptimal collateral venous drainage. Acute venous hypertension due to sinus occlusion was thought to be the cause of acute deterioration. (*continued*)

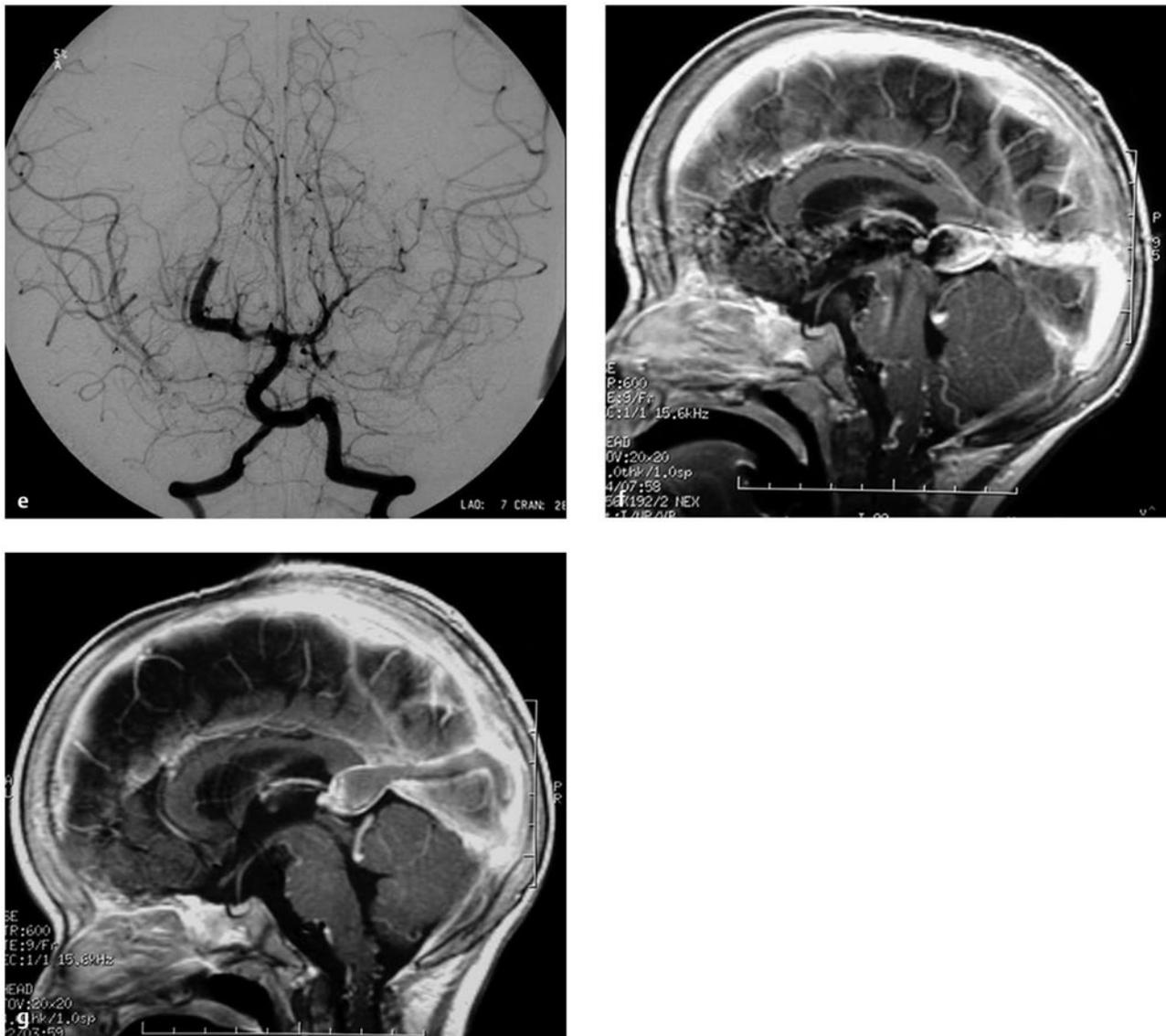


Fig. 69.3 (continued) (e) The patient underwent endovascular embolization with *N*-butyl-cyanoacrylate (NBCA), resulting in complete occlusion of the single-hole fistula. T1-weighted sagittal MR imaging with contrast (f) before and (g) after the embolization showing decreased congestion of the brain and thrombosis of the vein of Galen and embryonic falicine sinus. Note the increased cerebrospinal fluid space and decreased size of the veins in the posterior fossa after embolization. The patient was discharged neurologically intact without seizures.

with the heart failure because of a right-to-left shunt from a patent ductus arteriosus, from a patent foramen ovale, or from pulmonary hypertension that may be irreversible, even after treatment. A patent ductus arteriosus can worsen the clinical situation and may require cardiac surgery. Cardiac failure has been diagnosed prenatally in a few patients and is usually associated with major neonatal cerebral ischemia and encephalomalacia.

Cardiac manifestations have been reviewed for antenatally diagnosed VGAM.⁹ In the series of Rodesch et al⁹ of 18 patients with antenatally diagnosed VGAM, 17 were born with cardiac failure. During antenatal ultrasound examination, cardiac enlargement was noted in 4 of 17 patients. These 4 patients all had a low neonatal score because of systemic failure or because of encephalomalacia. Treatment was withheld in these 4 patients, and they soon died. The others were medically managed

and underwent embolization at between 2 and 13 months. Their neurologic outcome was reported to be excellent at 2-year follow-up. The antenatal diagnosis of VGAM is not an absolute indication for emergency embolization in the neonatal period. Macrocrania in uterus has no negative significance in our experience.

The pathophysiology of cardiac failure in neonates with high-flow AV fistulas starts with increased venous return and subsequent right-sided heart overload. The AV shunts therefore lead to right-sided heart dilatation, pulmonary arterial hypertension, and increased pulmonary blood flow. The resultant greater pulmonary venous return to the left side of the heart increases the left ventricular diastolic volume, which may be further increased by a patent ductus arteriosus if present. The increased left ventricular preload results in increased

myocardial oxygen requirements. Coronary perfusion to the left ventricle occurs mainly during diastole and depends on the systemic arterial–intramyocardial diastolic pressure difference as well as the duration of diastole. Therefore, a reduction in arterial diastolic pressure (as observed in an AV shunt), an increase in end-diastolic pressure (due to increased preload), and a reduction in the diastolic period (tachycardia) are all detrimental to myocardial perfusion and hence oxygen delivery, which precipitates left ventricular failure. Thus, even if only the right ventricle fails initially, biventricular failure frequently follows depending on the size of the left-to-right shunt.

The neonatal heart is limited in its reserve capabilities and cannot cope with the extra work imposed by the fistula. These factors explain the rapid progression toward cardiogenic shock observed in neonates with high-flow fistulas. Furthermore, the transition from a fetal circulatory pattern to an adult circulatory pattern is complex, and both the pulmonary circulation and the systemic circulation remain highly unstable during the first week after birth. This can explain a persistent transitional circulation with shunts through a patent ductus arteriosus and a foramen ovale and pulmonary hypertension, which both worsen the systolic and diastolic wall stress.

Hepatomegaly with hepatic dysfunction, prerenal azotemia followed by oliguria, and metabolic and lactic acidosis are also present in severe cardiac failure and are negative predictive factors.

At present, in utero diagnosis has become more frequent, and we have developed a multidisciplinary strategy to optimize the care of these challenging patients. After the diagnosis is made, usually by prenatal ultrasound, we obtain MR imaging in utero to confirm the diagnosis and search for any obvious brain damage. The mother then undergoes an evaluation by a pediatric cardiologist, which includes fetal ultrasound and echocardiography. Fetal echocardiography is performed when a VGAM is diagnosed prenatally primarily to assess the fetal heart size and determine the presence of associated heart defects. The fetal heart size is assessed by measuring the cross-sectional area of the fetal heart in a four-chamber view and the cross-sectional area of the fetal chest. Normally, the cross-sectional area of the fetal heart is one-third of the cross-sectional area of the chest. This ratio may be increased to more than one-half in a fetus with VGAM. When the ratio of the cross-sectional area of the fetal heart to the cross-sectional area of the chest is 0.5 or more, the mother is started on digoxin. This is given under cardiac monitoring at doses of 0.5 mg intravenously every 6 hours until a maternal serum digoxin level of close to 2 ng/dL is reached. At that point, the patient is switched to an oral maintenance dose of digoxin, usually about 0.5 mg twice daily, and a digoxin level of approximately 2 ng/dL is maintained until delivery.

Neonatal Care

When possible, the patient is born at our hospital and transferred to the neonatal intensive care unit for immediate evaluation by the pediatric cardiologist and intensivist. The opportunity is taken to obtain umbilical arterial and venous access, which is critical. If needed, respiratory support with positive-pressure ventilation or intubation is initiated. A cardiovascular examination, echocardiography, and transcranial ultrasound are obtained on day 1 of life. Heart failure, when present, is

managed with medications. If the patient cannot be weaned from ventilator support or intravenous medications or is progressing toward multiple-organ failure, then endovascular intervention to close as much of the fistula as possible and control the heart failure is considered. Otherwise, a stable patient is followed with a plan for treatment in 5 to 6 months. As our experience with newborns increases, our threshold for intervention has been lowered toward earlier intervention, which avoids the need to deal with a very sick newborn who has a greater likelihood of irreversible damage. We have found certain early echocardiographic findings to be prognostic indicators of the necessity of early intervention. In addition to generalized cardiomegaly and hypercontractility, these echocardiographic findings include pulmonary hypertension, frequently with suprasystemic pressure in the pulmonary artery as measured by tricuspid insufficiency velocity. There is persistent fetal circulation, with right-to-left shunting at the level of the patent ductus arteriosus and the patent foramen ovale. Almost all patients requiring neonatal intervention have dilatation of the ascending aorta and the carotid arteries, with Doppler findings of severe diastolic reversal of flow in the descending aorta. Patients with severe heart failure and pulmonary hypertension are maintained on mechanical ventilation, at times with the use of nitric oxide. They are started on intravenous inotropic agents, such as dopamine, dobutamine, and milrinone, as well as furosemide and digoxin. All patients undergo neuroimaging with MR imaging techniques, including diffusion-weighted imaging, MR angiography, and MR venography, before intervention. Neuroimaging assesses the brain parenchyma for underlying permanent damage or ischemic changes and delineates the vascular anatomy and venous outflow. High flow through the sinuses, without outflow restriction, also correlates with uncontrolled heart failure and the need for early intervention. Evidence of parenchymal damage is used for the prognosis and in the decision to proceed with or withhold treatment.

With the present availability of noninvasive imaging, there is no role for diagnostic angiography; the only reason to undertake invasive intervention is for emergent treatment, and this should be done in very specialized centers. All patients are treated with transarterial *N*-butyl-cyanoacrylate (NBCA) liquid embolic material, which is used to target the fistula sites of the malformation. Although in the past we have used transumbilical access to the cerebral circulation,²⁴ at present we routinely use ultrasound-guided percutaneous femoral artery access. Transvenous access is used in older children who have no femoral access or the residual arterial supply is collaterals, distal perforators secondary to proximal pedicle occlusion versus fistula closure. In neonates, the venous approach was not necessary in any cases. The goal of embolization in the neonate is to reduce AV shunting to permit control of the CHF.

Endovascular Treatment

The treatment of a newborn in heart failure must be very efficient, with the extremely limited use of liquids and contrast material, which may be restricted by the patient's weight (up to 10 mL/kg). If the treatment goal cannot be achieved in one session, the patient will undergo a second session of treatment another day. After the resolution of severe heart failure, patients return for further treatment sessions at approximately 6 to 8

months of age or earlier, if necessary. The final goal is complete obliteration of AV shunting without neurologic injury.

In 2012, we reported our results of the management of 16 patients who presented to the INN during the antenatal or neonatal period with a diagnosis of VGAM. Of 16 patients, 10 had an antenatal diagnosis of VGAM by prenatal ultrasound in the third trimester. VGAM was diagnosed in the remaining 6 patients after birth. Of the 16 patients, 7 responded to medical management in the neonatal intensive care unit, were discharged from the hospital, and returned for endovascular treatment at a later date. Nine patients required endovascular intervention because of refractory heart failure within the neonatal period. All 9 patients had a choroidal-type VGAM and required treatment within the first 10 days of life. Associated fetal cardiac defects were seen in 4 patients, who had sinus venosus, atrial septal defect, or a mild aortic coarctation (1 patient). Of 8 patients, 5 required more than one endovascular treatment session during the neonatal period to adequately control heart failure. Control of heart failure was achieved in 8 of 9 patients. One premature baby who weighed 1.5 kg died after treatment because of diffuse intracranial hemorrhage. One technical complication occurred, in which a microcatheter rupture resulted in stroke and a permanent neurologic deficit of mild hemiparesis. After endovascular embolization, routine cross-sectional imaging demonstrated that 3 patients had asymptomatic intracranial hemorrhage. These included 2 patients in the series who were treated despite parenchymal abnormality on pretreatment MR imaging. In these patients, asymptomatic petechial hemorrhagic conversion occurred in the preexisting area of diffusion abnormality. After embolization, 8 of 9 patients were managed medically and discharged from the hospital on oral medications.

Long-term Outcomes

Of the 8 patients who survived the neonatal period, angiographic obliteration has been documented in 6 at an average age of 20 months after an average of 4.2 treatments (► Fig. 69.1). The remaining 2 patients have an estimated 95% closure of the AV shunting with a significant reduction in the size of the vein of Galen. Clinical outcomes are as follows: One premature baby died. Two of the 8 patients have minor neurologic deficits. In one, a microcatheter rupture resulted in an intraprocedural left middle cerebral artery stroke during his second treatment. He has a mild left hemiparesis and undergoes physical therapy. The other patient had focal posterior cerebral artery territory infarcts on pretreatment MR imaging because of hypotension in the neonatal period and has mild motor and language delay. One of the 8 patients has severe developmental delay and seizures. This patient had bilateral laminar necrosis on pretreatment MR imaging. Five of the 8 surviving patients have normal neurologic development and are achieving normal developmental milestones. In our series, one patient developed chronic occlusions of the femoral arteries with the formation of collaterals seen on angiography. There were no clinical sequelae. There are also technical considerations in the embolization of these lesions. The usefulness of the transvenous approach in neonates has been reported, given the difficulty with transarterial access.^{17,29} In true VGAM, the transvenous approach may be a viable option. However, it has been our experience that a vein of Galen malformation cannot be distinguished from a vein of

Galen dilatation with normal cerebral veins draining into the aneurysm with certainty in a neonate. A transvenous occlusion of the aneurysm in a patient with a vein of Galen dilatation can have devastating consequences, such as postprocedure venous infarct and hemorrhage, by obliterating the venous outflow of the normal brain. A recent literature review of VGAM treatment supports this, with patients treated transarterially exhibiting a higher rate of “good” clinical outcome.³⁴ Although in the past we reported the use of a transumbilical approach in neonates with VGAM,²⁴ since the initiation of the use of ultrasound for femoral artery cannulation, we have had no failures with this approach. A unique complication of femoral artery occlusion due to repeated femoral artery access occurs in pediatric patients in comparison with adults. After the procedure, careful compression and hemostasis are essential because the long-term patency of the vessels may become compromised. With advancements in our treatment strategy over the past two decades, as discussed above, our mortality rate has dropped to 11% in this current series. Normal neurologic outcome has been achieved in 66.7% of patients and mild delay in 11%, with a good outcome rate of 77.8%.¹⁰ The importance of an interdisciplinary team starts at the very time of diagnosis. In utero management by an experienced high-risk obstetric team and pediatric cardiologist is essential. Fetal and neonatal echocardiography can identify patients in whom refractory heart failure is likely to develop. At present, because of significant advances in endovascular techniques, it is possible to intervene much earlier, before end-organ damage occurs.

69.3.2 Infant Hydrodynamic Disorder

In infants, the presenting symptoms are usually caused by hydrodynamic disorders. Hydrodynamic disorders, however, can manifest in fetuses, neonates, and infants. They manifest as macrocrania, which results from enlargement of the cerebrospinal fluid space, hydrocephalus, and increased intracranial pressure and can be associated with developmental delay and mental retardation. Decompensation can occur when cranial sutures close. The drainage of the AV shunt increases the pressure in the torcular and superior sagittal sinus, thereby creating a hemodynamic obstacle to the cortical and deep venous drainage of the brain. This condition is aggravated by the fact that the venous drainage of the brain converges to the torcular at this age. Further compromising the cerebrospinal fluid drainage, the pacchionian granules do not mature until infancy. Distal venous stenosis or secondary venous occlusion can occur and further compromise the cerebral venous drainage. The direction of flow in the cerebral veins is usually reversed and rerouted toward the cavernous sinus and ophthalmic veins, causing dilatation of the facial veins or epistaxis, or to the basisphenoid sinus and pterygoid veins. If these alternative pathways of venous drainage are not yet well developed, cerebral venous congestion can lead to brain edema, hypoxia, and hydrocephalus, aggravating neurologic conditions.¹¹ If the sylvian veins and the cavernous sinus develop with adequate extracranial outflow, spontaneous stabilization of the hydrodynamic disorder can occur.

Hydrocephalus results from the impairment of cerebrospinal fluid resorption due to venous hypertension. Although the VGAM may compress the aqueduct of Sylvius, obstructive hydrocephalus is rare. Ventricular shunting interferes with the water balance between the extracellular and intravascular compartments and

may cause brain edema, enlargement of the VGAM, seizures, subdural hematoma, and overshunting with slit ventricles.

69.4 Natural History

69.4.1 Cerebral Calcification

Cerebral calcifications are typically bilateral, symmetric, and located in the transcerebral venous watershed area between the superficial and deep venous system. When present, cerebral calcifications are objective anatomical evidence of a venous hypoxic disorder and its hydrodynamic consequences. Calcification is often associated with subependymal brain atrophy and may secondarily produce seizures.

69.4.2 Dural Sinus Occlusion and Venous Hypertension

Progressive dural sinus occlusion is common in the evolution of VGAM, but its cause is unknown. This phenomenon is not specific to VGAM but is frequently seen in high-flow fistulas in young children. We are not aware of any experimental studies that have investigated the etiology of progressive sinus occlusion. We speculate that this is related to a combination of underdevelopment of the jugular bulb, abnormal skull base maturation due to macrocrania, and high-flow angiopathy of the venous system due to high-flow fistulas that may lead to kinking or thrombosis at the tentorial or dural edge at the skull base. The symptoms depend on the timing between sinus occlusion and capture of the sylvian veins by the cavernous sinus and on the patency of the jugular bulbs and veins. When the jugular bulbs are occluded, the veins of the foramen ovale or the ophthalmic veins will drain the cavernous sinus, which may cause dilatation of the facial veins. If both the VGAM and the brain drain into the same cavernous sinus, facial vein dilatation will be more prominent and epistaxis can occur because of nasal vein congestion. If collateral venous outlets are insufficient, cerebral pial venous congestion may develop. The long-term result of pial venous congestion is chronic cerebral ischemia, manifested by development of calcifications and the peculiar appearance of the chronically congested cortical veins. If further outflow restriction of the venous drainage of the VGAM occurs, pial cortical venous reflux will develop, which can cause acute focal neurologic deficits, seizures, and hemorrhages. When these occur, they represent rare examples of hemorrhages seen in children or young adults with true VGAM.

Prolapse of the cerebellar tonsils is a manifestation of infratentorial pial venous congestion due to sinus occlusion. If the prolapse has not been present for a long time, it may disappear with occlusion of the AV shunts. Prolapse of the cerebellar tonsils usually does not cause any specific symptoms at this age. The prolapse is not related to a global increase in intracranial pressure and is not an indication for emergency ventricular shunting, but rather for endovascular embolization to decrease venous hypertension.

69.4.3 Hemorrhage

Intracranial hemorrhage is rare but possible in patients with VGAM. Intracranial hemorrhage can occur if venous stenosis or

occlusion reroutes the venous drainage of the AV shunt into pial veins. This usually occurs in older children and young adults as a secondary manifestation. We have not encountered hemorrhage as the initial presentation in true VGAM. In contrast, hemorrhage is a frequent manifestation of VGAD. Most cases of so-called vein of Galen malformation presenting with hemorrhage in the literature are actually VGAD, not true VGAM. VGAM can also bleed after partial treatment with venous outflow occlusion, which is more common after transvenous than transarterial embolization. Other types of bleeding, such as hemorrhagic infarction, intraventricular hemorrhage, and subdural hematoma, may occur following ventricular shunting or transvenous embolization.

69.5 Treatment

Depending on the patient's age and the type, onset, and predominant symptoms of VGAM, the objectives of treatment will vary. A major breakthrough in treatment began in the early 1980s with endovascular embolization in the management of VGAMs.¹²⁻¹⁶ Before the introduction of endovascular embolization for the treatment of VGAM, surgery had been performed with uniformly poor results.¹⁷ Mickle and Quisling¹⁸ introduced the neurosurgical transthoracic venous approach to control severe CHF in 1986, and Lasjaunias et al reported the first complete transarterial occlusion and cure in 1989.¹⁹⁻²¹ If treatment is properly timed and performed by a group well trained in pediatric interventional neuroradiology and endovascular neurosurgery, embolization of VGAM is the present treatment of choice and can lead to good clinical outcomes. Medical, surgical, and/or radiosurgical treatment is also used, either alone or combined with endovascular therapy. The indication for radiosurgery is limited to the last stage of treatment for a small residual in older children.

69.5.1 Indications and Goal

The ultimate goal of treatment for VGAM is complete obliteration of the lesion leading to normal development of the patient without neurologic deficits. The immediate treatment goal, however, is different and depends on the age of the patient. The primary goal of treatment in neonates is obliteration of the major portion of the fistulas to allow the resolution of CHF. The combination of neonatal macrocephaly or moderate hydrocephalus with CHF that is not life-threatening does not mandate urgent treatment. Conversely, if significant brain damage is demonstrated by computed tomography (CT), ultrasound, or MR imaging, treatment is not indicated because the clinical outcome is poor even if the lesion is anatomically cured (► Fig. 69.4).²²⁻²⁴ The extent of angiographic evaluation before treatment should be limited in neonates because they usually have compromised cardiac and renal function and cannot tolerate a significant volume and contrast medium load. Immediate complete occlusion of the malformation is not always possible, but it is usually not necessary in neonates to achieve the immediate goal.

For infants and children, the immediate goal is to restore the normal hydrovenous equilibrium to permit normal development and at the same time to obliterate the lesion. Our special interest in patients at this age is to avoid ventricular shunting

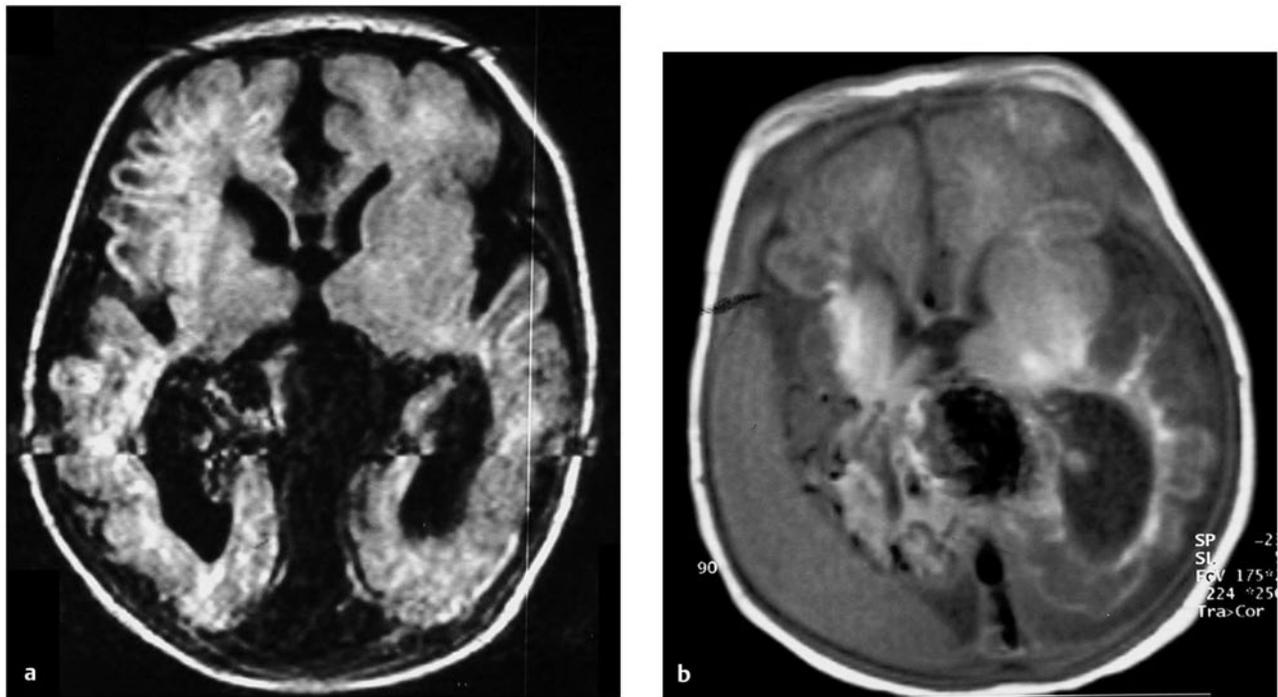


Fig. 69.4 This male patient presented with severe congestive heart failure (CHF) at birth. (a) FLAIR (fluid-attenuated inversion recovery) magnetic resonance (MR) imaging at 1 day old demonstrates severe brain tissue loss and midline vascular malformation with a dilated vein of Galen. The patient underwent transarterial and transvenous embolization at 2 days and at 12 days old at an outside institution with technical success in partial obliteration of the vein of Galen aneurysmal malformation, although treatment was not indicated because of significant brain damage. (b) T1-weighted MR imaging at 25 days old demonstrates the progression of brain atrophy and a subdural fluid collection. *Arrow* indicates coils in the draining vein. At 18-month follow-up, the patient had no CHF but was on tracheostomy and tube feeding with spastic quadriplegia. The patient underwent embolization at this time with complete occlusion of the malformation and relief of apparent headaches.

by performing timely endovascular treatment. Therefore, if the head circumference increases rapidly, or if there is MR imaging evidence of increased intracranial pressure, or if the clinical follow-up demonstrates a significant developmental delay, then urgent embolization should be performed. In our experience, transarterial embolization is effective in decreasing the venous pressure and relieving the clinical symptoms of the hydrodynamic disorder. However, embolization should be performed before the full development of hydrocephalus and its clinical symptoms, even if the VGAM fistulas cannot be completely occluded. If endovascular treatment is performed after the full development of hydrocephalus, the effect of embolization is usually insufficient, and a ventricular shunt should then be considered. Of note, if further endovascular treatment is considered, embolization should not be performed for at least a few days after the placement of a ventricular shunt to avoid the risk for upward cerebellar herniation secondary to a rapid decrease in the supratentorial pressure.

If cerebral pial venous congestion develops and leads to acute focal neurologic deficits, seizures, and hemorrhage, emergency endovascular treatment should be performed to reduce cerebral venous hypertension. The results of embolization should be rapidly detectable clinically and recognizable by the progressive disappearance of the facial venous collateral circulation

and neurologic improvement. Dural AV shunts may develop within thrombosed portions of the sinus. They usually disappear following complete obliteration of the VGAM.

For patients who were referred late for treatment with already impaired neurologic function or severe mental retardation, we still perform endovascular treatment to improve their quality of life and can usually achieve satisfactory results, even though the lesion is not completely occluded. A determination of the end point of the treatment is based mainly on the draining pattern of the brain and the malformation, which is related to the degree of development of the cavernous sinus, maturation and patency of the jugular bulb and internal jugular veins, and patency and functional efficacy of the embryonic sinuses.

In summary, indications for early intervention include the following: (1) unstable or progressive cardiac failure despite adequate medical treatment, (2) the recognition of developmental delay or venous ischemic changes, such as calcifications, (3) the development of significant macrocrania, and (4) pial venous hypertension. During conservative follow-up, monthly measurement of the head circumference and weight and 3-month follow-up MR imaging should be obtained. If MR imaging shows any sign of the development of hydrocephalus or ischemic changes in the brain parenchyma, endovascular treatment should be performed without delay.

69.5.2 Evaluation

The evaluation of a VGAM should include the following: (1) clinical history and physical examination, (2) assessment of renal and liver function, (3) transfontanel ultrasound to evaluate the size of the ventricles and brain parenchyma, (4) cardiac ultrasound to assess cardiac function and to evaluate associated cardiac malformation, and (5) MR imaging of the brain to obtain morphological information regarding the lesion and the brain parenchyma. Angiography in the neonatal period should be obtained only when embolization is considered at the same setting. In view of the limited arterial access, diagnostic angiography alone is not indicated. The weight and head circumference of the patient should also be carefully followed before and after treatment.

The indication for, and timing of, treatment should be decided based on a careful assessment of the neurologic symptoms, growth and development, cardiac and other systemic manifestations, and imaging studies of the VGAM and brain parenchyma. If the patient is clinically stable with or without cardiac medication, it is preferable to delay the treatment until 5 to 6 months of age.

69.5.3 Endovascular Treatment

The endovascular treatment of VGAM is performed either by occluding the fistula sites via a transarterial approach or by occluding the ectatic vein via a transvenous approach. Transfemoral transarterial embolization is our first treatment choice. A transumbilical artery approach is possible for newborn patients and sometimes preferable because of the small size of the femoral artery.²⁵ The risk for immediate or delayed hemorrhagic complications is significantly less with transarterial embolization. To achieve satisfactory results, proper patient selection is mandatory. If the venous route is under consideration, one must be absolutely certain that the dilated vein is not connected to normal cerebral veins.

A 4F sheath is used for transfemoral access. Pretherapeutic angiography is performed with a 4F catheter and a low-osmolality and nonionic contrast material. The left or right vertebral artery injection in the frontal projection is usually the best first study to identify the largest fistula, which should be the first target for embolization. In neonates and infants, angiographic study before treatment should be limited because of the small body weight. Most neonates can tolerate 4 to 8 mL of contrast material per kilogram of body weight well. The total amount of contrast material that a patient can tolerate varies depending on the duration of the entire procedure and on urinary output. In older patients, full angiography can be performed before the treatment.

Following diagnostic angiography, transarterial embolization is performed with a flow-guided microcatheter placed through the 4F guiding catheter. Our first choice of embolic agent for transarterial embolization is NBCA. It is important to occlude the fistula site itself to avoid collateralization to the fistula. Complete closure of the malformation can be accomplished in one session, particularly in patients with a mural-type VGAM. We have not experienced perfusion pressure breakthrough phenomena in our series. Following total or nearly total occlusion of the fistulas, progressive thrombosis and shrinkage of the

ectatic vein are observed on CT or MR imaging over several weeks. In patients with a more complex arterial supply, especially those with choroidal VGAMs, embolization should be staged. The clinical symptoms usually improve even after partial embolization.

Transvenous embolization of a VGAM may be accomplished by either a percutaneous transfemoral or a transtorcular approach. The transtorcular treatment can be performed by either surgical exposure of the torcular or ultrasound-guided percutaneous penetration of the overlying dura with a needle.²⁶ Reduction of AV shunting is achieved by packing the venous pouch with a variety of materials, including coils,^{26,27} nylon,²⁷ and balloons.²⁶ Several sessions of treatment may be required to achieve a satisfactory response.^{18,28,29} The extent of the embolization may be monitored during the procedure by the injection of contrast transarterially or directly into the pouch, or alternatively by the measurement of intra-aneurysmal pressure.³⁰ One may also consider angioplasty and stenting of the dural sinus for progressive sigmoid/jugular occlusion and severe intracranial venous hypertension when endovascular embolization does not improve the symptoms. The long-term durability of dural sinus stenting is unknown.

The venous approach is technically easier but in our experience leads to less favorable clinical outcomes compared with transarterial embolization. Long-term neurologic outcome after venous embolization is less clear, and venous embolization is contraindicated in VGAD associated with a pial AVM.³¹ It is not always easy to differentiate between a VGAM and a VGAD with a fistulous pial AVM. Even with a true VGAM, sudden complete occlusion of the draining vein may cause venous infarction or hemorrhage. A combination of transarterial and transvenous embolization may be beneficial for certain cases in which complete occlusion of the fistulas cannot be achieved by the transarterial approach alone. In such cases, transvenous embolization is performed at the end to close the small residual fistulas and completely obliterate the malformation.

69.5.4 Medical Treatment

The most important medical treatment in cases of VGAM is for cardiac failure in the newborn. If cardiac failure can be controlled with medical treatment, endovascular treatment should be delayed until the patient is 5 to 6 months old, when endovascular treatment is much easier and safer and carries less risk for ischemia of the leg following a transfemoral approach compared with the newborn period. The management of cardiac failure consists mainly of diuretics, pressors, and oxygenation with or without assisted ventilation, depending on the severity of the symptoms. Cardiac output can be improved by increasing cardiac contractility with inotropic agents. The effect of digitalis in the hyperkinetic state due to AV fistulas remains controversial, although it is, in general, the main agent used to increase myocardial contractility. There is no clear evidence that the use of digitalis to further increase the contractility of already hyperfunctioning myocardium has any clinical benefit. In situations of severely compromised cardiac output, dobutamine and dopamine can be used to augment myocardial contractility. If a patient does not respond to maximal medical treatment, emergency embolization of the VGAM is indicated. The cardiac status

effectiveness is uncertain for high-flow fistulas of VGAM. The latency period is prohibitive in achieving the occlusion needed for the normal developing brain. Stereotactic radiotherapy may be useful in an older patient who has relatively slow-flow residual shunts after endovascular treatment.

69.5.7 Outcome

A review of the literature shows that the outcome of both conservative management and surgical treatment has been poor, particularly for newborns and infants. In the review of 245 cases of Johnston et al,¹⁷ overall mortality was 91.4% in the neonatal group, with the majority of patients dying within 1 week of diagnosis or treatment. Mortality was 100% (12 patients) without treatment, 95% (38/40) with medical treatment, and 82% (14/17) with surgical treatment. In patients 1 to 12 months of age, overall mortality was 48%, and 50% of the survivors were neurologically impaired. Mortality was 73% (8/11) without treatment, 33% (2/6) with treatment only for CHF, 64% (7/11) with shunt placement only, and 32% (13/41) with direct operation. These cases most likely include a significant number of pial AVMs with VGAD, which are poor surgical candidates, and more mural-type VGAMs than choroidal-type VGAMs.

In the review of cases involving children 1 to 5 years of age of Johnston et al, the overall mortality was 42% (13/31), 67% (4/6) without treatment, and 35% (6/17) with direct surgery. Again, the cases likely include a significant number of pial AVMs with VGAD, especially in the group with no treatment.

Many survivors of any modality of treatment had significant neurologic deficits in all age groups.

Spontaneous thrombosis of the venous pouch and/or its outlets has been rarely reported (► Fig. 69.5).³⁴ It appears to occur more frequently in mural-type than in choroidal-type VGAM. It may be associated with increased intracranial pressure and/or venous ischemic episodes.

69.5.8 Neurologic Outcome after Embolization

In our surviving group of patients, 74% are neurologically normal. Among 193 patients, 20 (10.8%) have a severe neurologic or cognitive handicap. Some of them were in an irreversible state when they were referred to our center, but for the other patients a poor outcome was not anticipated.³⁵

69.6 Conclusion

An improved understanding of the clinical, anatomical, and pathophysiologic features of VGAM and the advent of endovascular embolization as primary therapy have significantly improved the formerly poor prognosis of VGAM. The majority of children can now survive with normal neurologic development after proper endovascular treatment. There is now no indication for VGAM surgery as the primary treatment modality. In addition, ventricular shunting can be avoided with timely embolization.

Pearls

- Diseases that cause enlargement of the vein of Galen include VGAM (enlargement of the median vein of the prosencephalon); VGAD (transvenous embolization is contraindicated), consisting of pial AVMs or dural AV fistulas; and VGV.
- The differentiation between a VGAM and a VGAD-associated pial AV fistula is based on the presence of venous reflux to normal veins and transmesencephalic feeders, and on the location of fistulas.
- There are two types of VGAM, choroidal and mural. Choroidal VGAMs are characterized by multiple high-flow fistulas, are present in neonates with severe heart failure, and are more difficult to treat. Mural VGAMs are characterized by one or a few fistulas, present in infancy as a hydrodynamic disorder, and are easier to treat.
- Indications for urgent treatment (treatment should be delayed until 5 to 6 months of age if possible) include CHF refractory to medical therapy, progressive macrocephaly, developmental delay, the development of hydrocephalus or calcification, and the development of neurologic symptoms.
- The venous drainage of the malformation and normal brain is the most important factor influencing the clinical presentation and long-term prognosis.
- In terms of treatment, heart failure requires medical treatment. Transarterial embolization is the first choice. Transvenous embolization is indicated in limited cases. Surgery is not indicated as a primary treatment. Radiosurgery is sometimes indicated for older children with a small residual.
- The hydrocephalus associated with VGAM is usually nonobstructive. Shunt surgery should be avoided if possible. Timely embolization often obviates the need for shunt surgery.
- Transarterial embolization for VGAM requires a transfemoral transarterial approach, a transumbilical artery approach for neonates, angiography at the time of treatment, a limited angiographic study (vertebral injection) for neonates, and flow-guided microcatheter embolization with NBCA (limited indication for coils).
- Transvenous embolization for VGAM requires a transfemoral transvenous or a transtorcular approach with guidewire-assisted microcatheter and coil embolization. It is usually reserved for the last stage of treatment to obtain complete obliteration.

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70 Pediatric Spinal Vascular Malformations

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Spinal vascular malformations are a distinctly rare but important pathologic entity in the pediatric population. From low-flow lesions like cavernous malformations to larger, high-flow lesions like juvenile arteriovenous malformations, significant variability occurs that requires a neurovascular team approach to management. Although these conditions are quite rare, with some estimates of less than 1 in a million persons,¹ the morbidity associated with the disease process can be significant. Presentations in the child population are often acute and dramatic.²⁻⁴ However, with appropriate management, patients can be treated with potential cure and improvement of neurologic status.

The first description of spinal vascular malformations was made by Virchow in 1865.⁵ At that time, they were felt to be neoplasms of the spine. The first surgery for a spinal vascular malformation, in a 13-year-old boy, was reported in 1912 by Charles Elsberg.⁶ The patient's condition did not improve after surgery. Later attempts concentrated on dural arteriovenous fistulas with venous stripping, but successes were relatively few. A spinal vascular malformation was first imaged in 1927 by Perthes, who used Pantopaque myelography.^{5,6} A true understanding of this class of disorders and their anatomy began with the use of spinal angiography in the 1960s.

In this chapter, we discuss the different anatomical types of spinal vascular malformations, highlighting their diagnosis and treatment. We also address syndromes that can be associated with these malformations. It should be noted that numerous classification systems have been used for spinal vascular malformations, mostly based on anatomical considerations. The most frequently used systems divide vascular malformations with shunting into four types: type I, spinal dural arteriovenous fistula (AVF); type II, intramedullary arteriovenous malformation (AVM); type III, juvenile diffuse AVM, or Cobb syndrome; and type IV, perimedullary AVF (► Fig. 70.1). Spetzler et al have recently added the conus AVM as a separate entity.⁷ Type I spinal dural AVF, although the most common type in adults, is an acquired lesion and is not found in children with any frequency.³ Cavernous malformations (CMs) are discussed in detail separately.

70.1 Spinal Intramedullary Arteriovenous Malformations

Intramedullary AVMs (type II) are true intramedullary malformations with a nidus interposed between multiple feeding arteries and draining veins that involve the substance of the spinal cord.⁶ Often referred to as glomus AVMs, these lesions are high-flow and high-pressure systems with an arterial supply derived from the anterior and/or posterior spinal arteries (► Fig. 70.2).

Uncommon in the general population, spinal AVMs in children account for a small percentage of the cases of this rare disease.^{3,8} The morphology of the malformations does not differ from that of the adult lesions per se, but the presentation and morbidity can differ. These are important clinical entities

because they produce considerable morbidity and may even be fatal if left untreated.

Treatment strategies are unique because pediatric diseases carry a complex set of variables that must be incorporated into treatment planning. In the later pediatric presentation, the disease features tend to more closely resemble those of the adult disease process, so it is postulated that the early pediatric presentation may be a severe form of the adult disease process.²

Like perimedullary fistulas, juvenile-type AVMs in the pediatric population are seen more often in boys than in girls.^{2,3} Pediatric intramedullary AVMs more often present with a history of progressive and fluctuating myelopathy and with episodes of acute neurologic deterioration secondary to hematomyelia.^{2,3} The lesions often involve the dorsal thoracic spine or conus medullaris.⁸ Some authors advocate placing conus medullaris AVMs in a distinct category.⁹

Unlike type III AVMs (spinal arteriovenous metameric syndrome [SAMS], or Cobb syndrome), which are extensive congenital vascular malformations, and type IV AVMs (perimedullary AVFs), which can be associated with syndromes like hereditary hemorrhagic telangiectasia (HHT), type II spinal AVMs are usually spontaneous.¹⁰

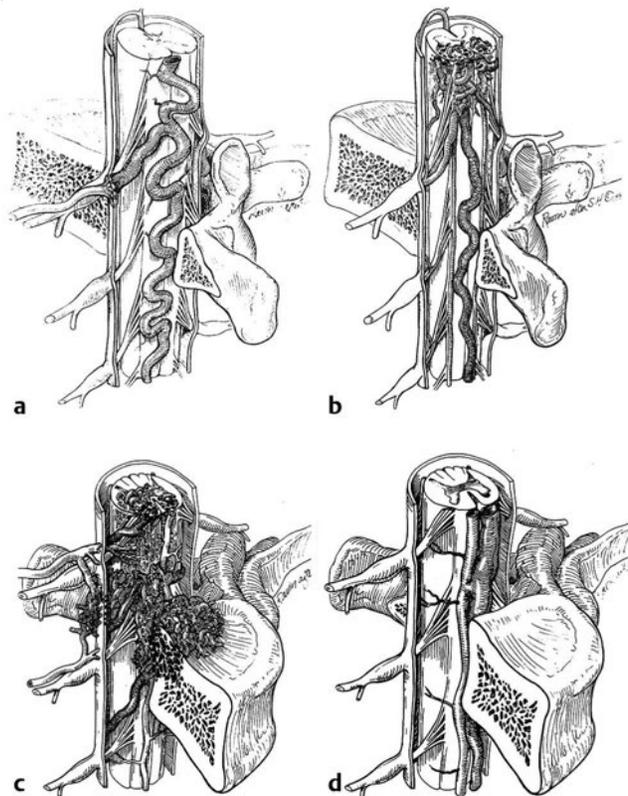


Fig. 70.1 Schematic representation of the classic four types of spinal vascular malformations. (Reproduced with permission from the American Association of Neurological Surgeons, Rolling Meadows, IL.)



Fig. 70.2 (a,b) Preoperative angiograms demonstrating a cervical intramedullary arteriovenous malformation (AVM). (c) Preoperative magnetic resonance image illustrating that the AVM is intramedullary. (d) Postoperative angiogram showing complete obliteration of the fistula.

70.1.1 Incidence and Prevalence

Spinal AVMs are underdiagnosed in the general population because of their variable and complex presentation, resulting in an estimation of the incidence of the disease rather than the true incidence. Estimations of 3.3 to 11% of all spinal cord lesions and 10% of all central nervous system (CNS) AVMs are reported in the current literature on the subject.^{11,12} These estimations are based on single-institution experiences with relatively small sample sizes, in large part as a consequence of the rarity of the disease.

Disease incidence is less frequent in the pediatric population. Berand in 1972 retrospectively reviewed 304 cases of AVMs of the spinal cord and found that 1.9% of patients were younger than 10 years and that 13% were younger than 20 years.¹³ Rodesch et al¹⁴ reviewed 155 patients with CNS arteriovenous shunts between the years of 1981 and 1999 (single institution) and found pediatric spinal AVMs to account for 5% of all CNS AVMs and for 20% of AVMs of the spine. Of the four types, types II and III are more commonly diagnosed in children and young adults.

70.1.2 Natural History and Presentation

Given the rarity of this disease, it is not commonly considered in the differential diagnosis, especially because of the lack of specific presenting clinical symptoms. Symptoms reported in the literature include neck, chest, and back pain; sensory and motor deficits; bowel and bladder dysfunction; headache; altered mental status; meningeal symptoms; and spinal bruit.^{3,15–18} Children more commonly present with an acute onset of symptoms than do adults.^{3,10} A review of 72 cases of pediatric spinal vascular malformation found a 52.8% incidence of acute presentation versus a 30.6% incidence of chronic, progressive symptom presentation for intramedullary spinal cord AVMs.³ An acute presentation often is a result of hemorrhage, either hematomyelia or subarachnoid hemorrhage.^{3,8}

The presenting symptoms can differ between extremely young children (younger than 2 years) and children younger than 15 years. Case studies of children younger than 2 years showed that they presented with a significantly lower incidence of hemorrhage, either hematomyelia or subarachnoid hemorrhage, than did children younger than 15 years.¹⁹ Cullen et al reported an incidence of hemorrhage of 23% in patients younger than 2 years with spinal AVMs versus an incidence of up to 67% in pediatric patients younger than 15 years.²

Initial estimates of disease progression and a poor prognosis for children with these lesions were likely influenced by the dural AVF literature.^{2,6} Unlike those who present with spinal cord AVFs, patients who present with hemorrhagic intramedullary AVMs usually improve without treatment. Cullen et al showed that 72% of pediatric patients improved, with only 20% showing worsening symptoms.² Interestingly, recurrent hemorrhage was seen in only 9% of patients.² These data support the concept that observation may be a reasonable option for patients in whom surgery is associated with unacceptable risk.

70.1.3 Treatment

The gold standard for the treatment of intramedullary AVMs remains microsurgical resection.^{6,8} Surgery can usually be approached with a posterior laminectomy or posterolaterally with a transpedicular exposure. General surgical outcomes for pediatric patients are better than those for their adult counterparts. A review by Kalani et al in 2012 reported the results of treatment of spinal AVMs at a high-volume center.⁸ Three of the patients were treated with surgery alone with good results.

Endovascular treatment provides an adjunct and, in some rare cases, an alternative to surgery for intramedullary and conus medullaris AVMs. If embolization is planned, some authors advocate spinal provocative testing to aid superselective angiography.^{8,20,21} In these cases, amobarbital (Amytal; Marathon Pharmaceuticals, Deerfield, IL) and lidocaine can be injected to test for clinical or neuromonitoring changes. If the test is negative, embolization can be completed with *N*-butyl-cyanoacrylate (NBCA) or Onyx (Micro Therapeutics [Covidien], Mansfield, MA). No clinical studies have compared the efficacy of embolization versus that of open microsurgical treatment.

At this time, the treatment for this complex lesion should begin with a high-quality spinal angiogram to assess its angioarchitecture.^{8,22} If there are pedicles to the AVM that can be traversed safely with a microcatheter without endangering the anterior or

posterior spinal arteries, an embolization can be attempted.²¹ Complete cures by embolization have been reported, although they are in the minority.^{8,22} After embolization, the majority of patients require surgical resection. The recommendation for resection should be made on individualized case-by-case basis. Although complete resection is the goal, the surgeon must recognize the limits of the resection and identify vessel loops that may leave a permanent deficit if chased into the spinal cord parenchyma. Velat et al described the resection of these lesions with a subtotal pial resection method, which devascularizes the AVM without violating the spinal cord parenchyma.²³ All patients should undergo postoperative angiography and, if possible, intraoperative angiography to document the extent of the resection.

Stereotactic radiosurgery currently does not have a treatment role in this patient population, considering the small size of the cord and the anticipated long life expectancy of the patients.¹⁰

70.2 Spinal Arteriovenous Metameric Syndrome/Cobb Syndrome

Spinal arteriovenous metameric syndrome (SAMS) is an extremely rare disorder that is nonheritable. It is characterized by a vascular malformation that extends beyond the spinal cord and involves the bones, paraspinal, skin, and soft tissues that arose from the same metamere^{24,25} (► Fig. 70.3). Cobb syndrome represents involvement of the entire metamere. The syndrome has previously been classified as a type III or juvenile AVM and is often referred to as an intradural–extradural AVM. Rodesch et al postulated that other genetic nonheritable syndromes, such as Klippel-Trénaunay syndrome and Parkes Weber syndrome, represent a lesser spectrum of these metameric disorders with multiple AV shunts.¹⁴

70.2.1 Incidence and Prevalence

The actual incidence of Cobb syndrome is difficult to estimate. The first report of the syndrome was in 1890.²⁵ It was not truly recognized until 1915, when Cushing deduced that Cobb had had a patient with an underlying spinal AVM in addition to the cutaneous findings. Overall, the complete metameric syndrome has been reported in fewer than 50 patients in the literature.²⁴ Like other pediatric spinal malformations, it shows a male predilection.³

70.2.2 Natural History and Presentation

Cobb syndrome presents equally with acute and chronic symptoms.^{4,24,26} Classically, acute presentations have a rapid monoparesis or paraparesis with loss of bladder or bowel function.^{25,26} Chronic symptoms include progressive back or radicular pain, progressive weakness and numbness, and bladder and bowel involvement. The natural history of Cobb syndrome remains unpredictable, with disease rapidly progressing in some patients and stabilizing in others.¹⁰ There are currently insufficient data to identify the prognosis accurately, although of the 5 identified patients treated conservatively, 2 worsened, 2 improved, and 1 stabilized.²⁴ In fact, Malis reported that “their rarity is perhaps the only favorable aspect of these lesions.”²⁷

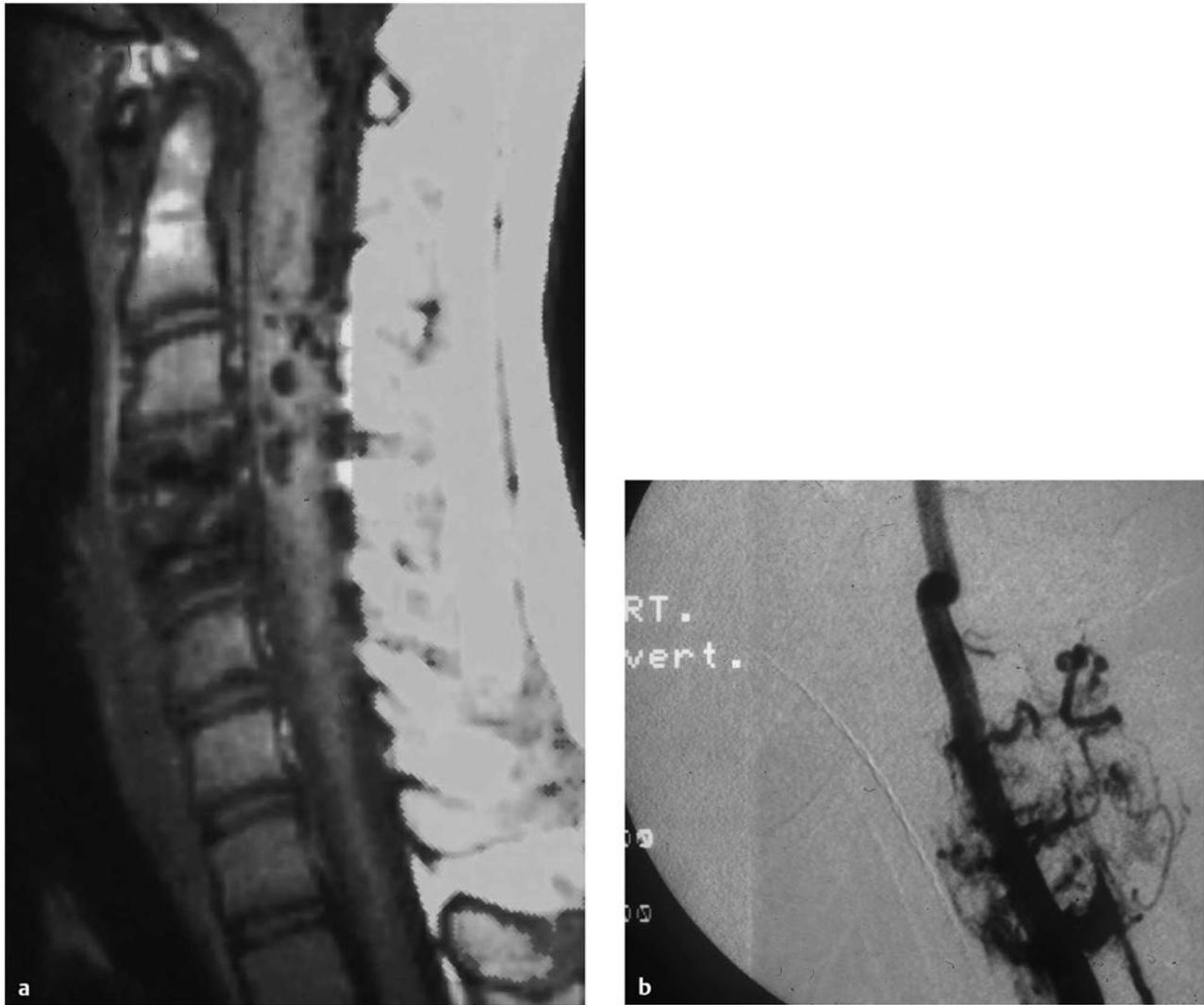


Fig. 70.3 (a) Magnetic resonance image and (b) angiogram showing a metamerically spinal arteriovenous malformation.

70.2.3 Treatment

The treatment of Cobb syndrome rarely results in complete resection of the AVM.^{8,24} Reports in the literature have described combined embolization and surgical resection resulting in complete cure, although they are rare.^{28,29} The goal for the treating physician should be to disconnect large feeding vessels with embolization and to combine this embolization with surgery to decompress the nerve roots and spinal cord, if possible.⁸ Often, embolization alone can reduce symptoms by decreasing venous hypertension and vascular steal. Additionally, some authors add corticosteroid administration and radiation treatment to surgery or embolization.³⁰ Clark et al published a review of patients with Cobb syndrome.²⁴ Seventeen patients underwent surgery alone, with seven reported improvements. Six underwent combined embolization and surgery, with five showing improvement. Overall, each case should be approached individually to assess what is best for the pediatric patient. Often, surgical resection should be avoided in a very young patient because of the potential for excessive blood loss.

70.3 Perimedullary Arteriovenous Fistula

Type IV AVMs are intradural, perimedullary, direct AVFs on the (usually ventral) pial surface of the cord between the anterior and/or posterior spinal arteries and the medullary veins (► Fig. 70.4). These fistulas were first described by Djindjian et al.³¹ Anson and Spetzler further subclassified them as types IV-A, IV-B, and IV-C based on their size and flow characteristics.⁷ Type A is a small fistula with minimal shunting and minimal venous hypertension, type C is a large fistula with high flow and significant venous ectasia, and type B is intermediate between type A and type C. Other authors have divided perimedullary fistulas into microfistulas (IV-A) and macrofistulas (IV-B and IV-C). A macrofistula in a pediatric patient is often correlated with HHT and may be the presenting manifestation of the disease.

70.3.1 Incidence and Prevalence

The incidence of perimedullary fistulas in the pediatric population is difficult to assess. Cullen et al estimated the total incidence of spinal arteriovenous shunts to be 1 in 1 million patients of all ages, with 20% of these patients in the pediatric age group.¹⁰ Du et al reported that 1.4% of all spinal vascular malformations are pediatric perimedullary AVFs.³

70.3.2 Natural History and Presentation

A review of 72 cases of pediatric spinal vascular malformation found the incidence rates of acute and chronic presentations to be equal in patients with perimedullary AVF.³ In most patients presenting with this type of spinal shunt, the manifestation of the fistula is related to venous hypertension and/or mass effect on the spinal cord.⁶ Although less often the case, subarachnoid hemorrhage may also occur. Perimedullary fistulas most commonly develop in the thoracolumbar region at the conus medullaris of the spinal cord.^{3,6,32}

The natural history of perimedullary AVFs is generally believed to be poor, even though there are no long natural history studies in pediatric patients. Most authors agree that the clinical course is one of progressive deterioration and recommend treatment. Additionally, any child presenting with a perimedullary AVF should be screened for HHT before treatment.^{3,8}

70.3.3 Treatment

The treatment of perimedullary AVFs must concentrate on disconnection of the point of arteriovenous shunting. Currently, most authors recommend endovascular embolization of the AVF initially with or without surgical resection.^{6,8} Embolization should concentrate on passing the catheter as close to the fistulous point as possible and injecting NBCA or Onyx through the fistula to the proximal venous drainage.^{8,32} In some cases, surgery may be required because of anatomical limitations or to remove mass effect from engorged venous structures.

Outcomes of the treatment of perimedullary fistulas are good to excellent in reported series, with improvement or stabilization noted in most patients. Rodesch et al in 2003 published their results on the embolization of spinal cord shunts.³³ Of the 69 patients, 20 were children, and 80% of the children showed clinical improvement. Cullen et al reported on 8 patients with fistulas who received endovascular treatment. Of the 8, 6 had 100% reduction of the fistula and the remaining 2 had 90% reduction.² Improvement of symptoms was noted in 6 of the 8, and the remaining 2 had stabilization of disease. Additionally, there have been numerous case reports of pediatric perimedullary fistulas treated with embolization or a combination of embolization and surgery that demonstrated improvement after treatment.^{32,34}

70.4 Cavernous Malformations

A CM is a thin-walled sinusoidal cavity with very slow to stagnant blood flow.^{35,36} These lesions were initially found only when they hemorrhaged into neural tissue. With the advent of magnetic resonance (MR) imaging, they are now often discovered incidentally. The MR imaging appearance of a CM is that of

a heterogeneous, reticulated, “popcorn-like” mass of mixed signal intensities that correspond to intralesional hemorrhage at various stages of evolution with a hypointense rim of surrounding hemosiderin-laden parenchyma (► Fig. 70.5). These lesions were initially referred to as angiographically occult vascular malformations because of the relative difficulty of visualizing them on a diagnostic angiogram.

The location of a CM may be intramedullary, extramedullary–intradural, epidural, or vertebral. We concentrate primarily on intramedullary CMs.³

70.4.1 Incidence and Prevalence

CMs have been reported in the literature since the late 1800s but were originally believed to be a rare lesion. With the advent of MR imaging, a more accurate incidence has been realized. Currently, CMs are thought to be present in 0.4 to 0.8% of the population.³⁷ Of this number, approximately 25% are in the pediatric patient group.³⁸ CMs are the most common CNS vascular malformation in the pediatric age group.^{3,38,39}

As in adult patients, the vast majority of CMs present in the supra- or infratentorial regions of the brain. Only 5% of CMs present in the intramedullary compartment, and, of that number, 10% occur in the pediatric setting.³⁹ In a review from 2001, roughly 12 pediatric CMs had been reported in the literature, with only small case series and reports published since that time.³⁹ Interestingly, a male preponderance of spinal CMs, at almost 2:1, is observed, although the number of cases is small. Some case series report more cervical lesions, whereas others suggest a thoracic majority.^{38–40} Spinal CMs have also been reported in the literature after spinal radiation.^{41,42}

70.4.2 Presentation

In 50 to 75% of cases, children present with an acute neurologic decline due to hemorrhage of the CM.^{38,40} In these cases, the patient will show acute myelopathy, with paraparesis or paraplegia and pain in the region. This is in contrast to adult patients, who often present with slowly progressive myelopathy.⁶ Children may have a slower, more chronic presentation, with progressive numbness, ataxia, hemiparesis, and ultimately pain. The typical time from symptom onset to diagnosis in children is 1 to 12 weeks.^{38,39}

70.4.3 Natural History and Treatment

The natural history of intramedullary pediatric CMs is not clearly understood, although estimates of the hemorrhage rate range from 1.4 to 1.7% per lesion per year.⁴³ In the adult literature, small numbers of patients followed conservatively with stabilization of symptoms have been reported.^{44,45} There are insufficient data in the pediatric population. The current recommendations are that treatment should be offered to any patient with neurologic decline or progressive myelopathy.

Currently, the only proven treatment for pediatric spinal CMs is complete and total microsurgical removal.^{6,45} Partial resection of a CM provides no benefit to the natural history of the lesion, with multiple repeated hemorrhages reported in the pediatric literature. Many authors recommend the use of intraoperative monitoring, although this has not been shown to improve outcomes.⁴⁶

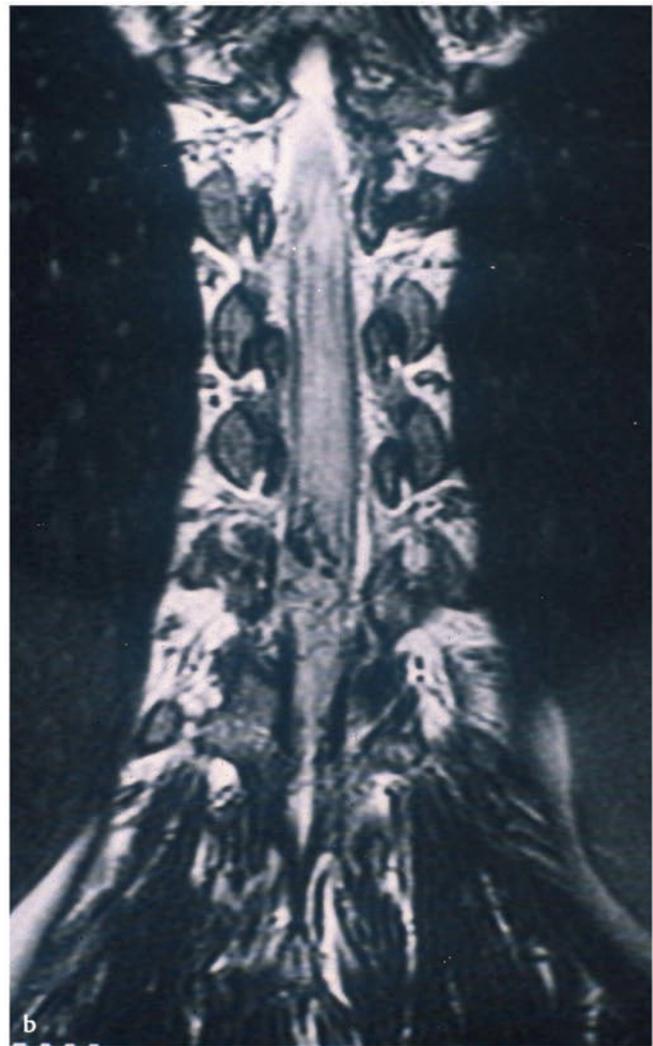
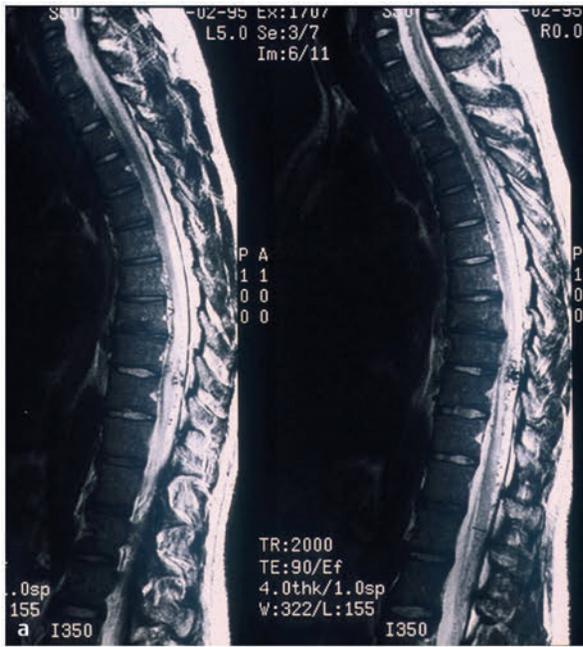


Fig. 70.4 (a,b) Magnetic resonance images showing a perimedullary fistula in a pediatric patient. (c) Angiogram confirming the diagnosis of perimedullary arteriovenous fistula.

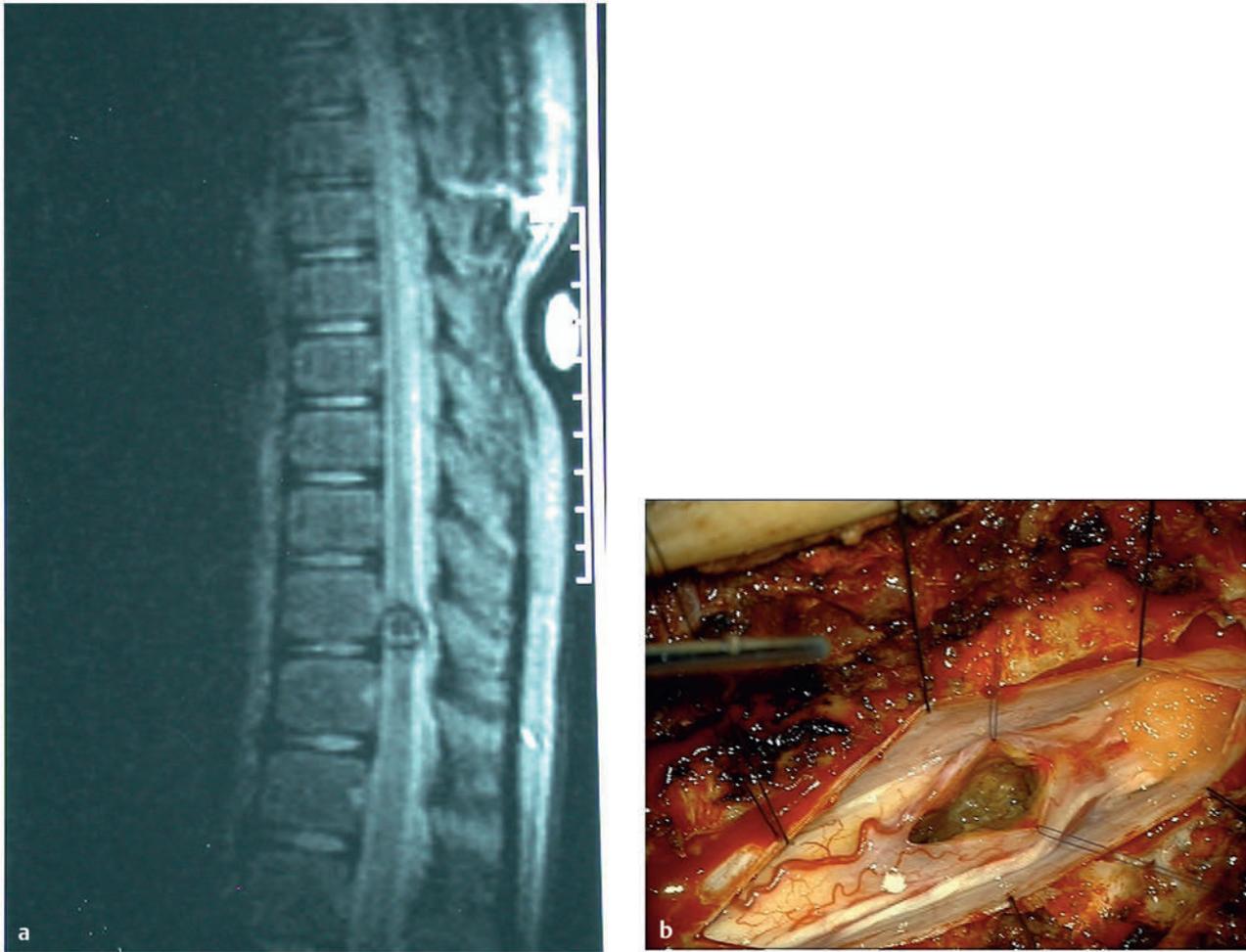


Fig. 70.5 (a) Magnetic resonance image of an intramedullary cavernous malformation (CM) in a young teenager. (b) Intraoperative image showing an intramedullary CM during resection.

Surgery proceeds similarly to adult cases. Most CMs can be reached by a standard laminectomy or laminotomy.⁴⁶ In some cases of more ventrally located lesions, a transpedicular approach with release of the dentate ligament can be utilized. In this age group, most surgeons avoid spinal fusion if possible.

The resection of a CM should take place at the point where it abuts the pial plane. If the CM is deep and midline, a midline myelotomy can be used.^{46,47} Entry into the dorsal root entry zone can be used in laterally oriented lesions. As in all spinal cord surgeries, entering the cord ventrally should be avoided if at all possible. Surgical results in the pediatric population are generally good, with one study reporting 83% of patients with symptom stability or improvement.³⁹ The degree of improvement is related to the patient's preoperative status, with early surgery before the development of severe deficits resulting in the best outcomes.

Stereotactic radiosurgery has not been established as an effective treatment for pediatric CMs.^{38,39} Additionally, the risks of radiation treatment to children far outweigh any theoretical benefit of the treatment.

70.5 Syndromic Associations

Several syndromes due to genetic mutations are associated with spinal vascular malformations. It is important to be familiar with these syndromes in the pediatric population because these patients typically present at an early age, some before 2 years of age.

The most common syndrome associated with spinal arteriovenous shunts is HHT.^{10,48} HHT is an autosomal-dominant angiodyplasia with variable expression and high penetrance.⁴⁸ The classic definition of the disorder includes the triad of epistaxis, telangiectasias of the lips and fingertips, and a family history. These patients have arteriovenous shunts in pulmonary, hepatic, and CNS circulations. The most common neurologic complications are often embolic as a result of pulmonary shunting, not primary CNS shunts. The incidence of the disorder is 1 in 5,000, although this may be an underestimation.¹⁰

An estimated 10 to 20% of patients with HHT have intracranial or intraspinal shunts.⁴⁹ Most authors recommend screening for intracranial vascular lesions within 6 months of the

diagnosis, although spinal screening is not routinely performed. In a review of 50 consecutive patients with HHT in France, 7 patients were found to have spinal arteriovenous shunts, all perimedullary macrofistulas.⁴⁹ Also, an analysis of 13 cases of spinal arteriovenous shunt in patients younger than 2 years showed 6 patients who had HHT, with 5 perimedullary fistulas and 1 spinal intramedullary AVM.² Patients who carry the diagnosis of HHT and present with spinal AVMs should be screened with MR imaging of the neuraxis to assess for other malformations.

Nonheritable syndromes are also associated with spinal arteriovenous shunts. Type III spinal malformation, or Cobb syndrome, is also termed spinal arteriovenous metamerism syndrome (SAMS).¹⁰ In a review of 13 spinal vascular malformations in patients younger than 2 years, 15% of patients had SAMS.² This disorder is described above.

Several additional syndromes are associated with arteriovenous shunts, namely Klippel-Trénaunay syndrome and Parkes Weber syndrome.¹⁰ Both syndromes are extremely rare and are due to a somatic mutation. Patients with Klippel-Trénaunay syndrome generally present with port-wine stains, varicose veins, and hypertrophy of bone and soft tissue. Parkes Weber syndrome results from a mutation in the *RASA1* gene and is characterized by multiple arteriovenous fistulas along with port-wine stains and overgrowth of a limb.⁵⁰ Some sources combine the two disorders. These patients often present with multifocal AVFs.

Since 1988, when Rigamonti et al found that 54% of CMs have a strong pattern of familial inheritance, it has been well known that familial CMs are not rare.⁵¹ They appear more often in Hispanic families, inheritance is autosomal-dominant, and affected persons present with multiple cerebral CMs.^{51,52} Three genes have been identified that are associated with familial CMs: *CCM1*, *CCM2*, and *CCM3*.^{52–55} Although the incidence of spinal CMs in cases of familial inheritance is unknown, studies have indicated that between 42 and 47% of patients may have coexisting intracranial and spinal CMs.⁵⁶ Some authors recommend adding spinal MR imaging to the work-up at initial presentation.

Pearls

- Although rare in the pediatric population, spinal vascular malformations pose a significant risk to patients who harbor the disease.
- Type I spinal dural AVFs, the most common type in adults, are not found with any frequency in children.
- Glomus AVMs present most commonly with hemorrhage and are treated with surgery with or without preoperative embolization.
- Type III juvenile spinal AVMs are extremely rare and generally not resectable with surgery.
- Type IV perimedullary fistulas present with chronic symptoms of venous hypertension and are amenable to endovascular treatment with or without surgical resection.
- Spinal CMs require surgical excision. Treatment is offered to any patient with neurologic decline or progressive myelopathy.

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Functional Disorders

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71 Evaluation of Intractable Epilepsy in Children

M. Scott Perry and Michael Duchowny

Epilepsy is the tendency to have more than one unprovoked seizure. The incidence of epilepsy is highest in the first years of life, and the majority of cases of childhood-onset epilepsy ultimately remit. Antiepileptic drugs (AEDs) remain the first line of treatment, with approximately 50% of patients achieving seizure freedom with their first medication trial and another 15% becoming seizure-free with a second medication.¹ Unfortunately, in 15 to 30% of patients, epilepsy remains medically intractable, defined as a failure of adequate trials of two tolerated and appropriately chosen AEDs to achieve seizure freedom.² Failure of therapy relies on the perception of the patient, parents, and physician that the medical treatment is not achieving an acceptable outcome. Infrequent seizures or a short duration of epilepsy does not exclude epilepsy from being intractable because both may still contribute to a significant medical risk. Even yearly seizures can exclude a patient from driving and adversely impact quality of life. Likewise, some patients present with frequent, disabling seizures for which intractability is rapidly determined, and surgical therapy may provide improvement in development. For those patients in whom intractable epilepsy develops, the evaluation can be extensive and is often carried out in specialized epilepsy centers well versed in the unique characteristics of pediatric epilepsy. The treatment strategies for such patients are complex and commonly include epilepsy surgery, neuromodulation, dietary therapy, and additional trials of medications used alone or in combination to achieve cure or palliation of symptoms.

71.1 Patient Selection

71.1.1 Pseudo-intractability

The process of labeling a child's epilepsy as intractable may seem straightforward based on the operational definition of failure of two prior AED trials; however, one must first determine that the AEDs used were appropriate for the type of epilepsy. For example, the idiopathic generalized epilepsies typically respond very favorably to adequate treatment, and most treatment failures result from an inaccurate diagnosis of the epilepsy type or a poor choice of medication.³ Persistent uncontrolled seizures in a patient with juvenile myoclonic epilepsy who is on carbamazepine monotherapy should not be unexpected because this drug may worsen clinical seizures. Likewise, it is important to carefully delineate whether medication failure is secondary to adverse effects or whether failure has occurred after maximum dosing titrations, because tolerability of the treatment is a prerequisite for efficacy. In rare circumstances, the sedative effects of an AED can lower the seizure threshold and paradoxically increase seizure frequency. In a recent review of patients with pseudo-intractable epilepsy who ultimately became seizure-free following medication changes, therapeutic errors (i.e., inadequate dosing of medications) were implicated as the cause of intractability in 48% of cases, followed by inaccurate

diagnosis of the seizure or syndromic type (47%) and medication noncompliance (14%).⁴

Equally important to ensuring that the treatments used were appropriately chosen and administered is demonstrating that the events being treated are epileptic in origin. Numerous behaviors incorrectly characterized as seizures can be encountered in children (see box "Childhood Disorders That May Mimic Epilepsy (p.932)"), and timely evaluation with video electroencephalography (EEG) can eliminate the need for an extensive evaluation of presumed intractable epilepsy.

Childhood Disorders That May Mimic Epilepsy

- Behavioral disorders
 - Staring spells, inattention
 - Psychogenic nonepileptic seizures
 - Breath-holding spells
 - Self-stimulatory behaviors
- Movement disorders
 - Focal dystonias
 - Nonepileptic myoclonus
 - Motor tics or stereotypies
- Cardiogenic disorders
 - Vasovagal syncope
 - Arrhythmia (long QTc syndrome)
- Other
 - Cataplexy

71.1.2 Assessment of Surgical Candidacy

Multiple historical features suggest a low likelihood of seizure remission. Most are recognizable early in the course of treatment, and the threshold for referring these children for further evaluation should be low (see box "Historical Features That Predict Evolution to Intractable Epilepsy (p.933)"). Childhood-onset epilepsy differs significantly from adult-onset cases, and several etiologies and syndromes are unique to the pediatric population (► Table 71.1). In many cases, the etiology may become clear only as the epilepsy evolves; thus, the history obtained by the clinician must include a detailed description of the seizures from the outset, such that idiopathic epilepsies of childhood, which ultimately remit, and those of symptomatic genetic origin (i.e., *SCN1A* mutations), which are unlikely to benefit from surgical therapy, are considered in the correct context. At the same time, there are several pediatric epilepsy syndromes and etiologies for which surgical therapy is especially efficacious and should be considered early in the course of treatment. Lastly, infants and young children differ in that catastrophic presentations of epilepsy may require more urgent surgical evaluation to prevent epileptic encephalopathy and loss of neurodevelopmental status.

Table 71.1 Intractable epilepsy syndromes that may not benefit from surgical therapy and etiologies that respond favorably to surgery

Syndrome	Clinical findings	Recommended testing
Dravet syndrome (severe myoclonic epilepsy of infancy)	Frequent or prolonged febrile seizures in infancy Myoclonic and hemiclonic seizures after the age of 1 year Developmental regression after onset	<i>SCN1A</i> gene testing
Epilepsy and mental retardation limited to females	Frequent febrile seizures in infancy Frequent seizure clusters with tonic or generalized tonic-clonic seizures Myoclonic seizures less often than in Dravet syndrome Variable developmental delay	<i>PCDH19</i> gene testing
CDKL5 syndrome	Early onset of infantile spasms Evolution to multiple seizure types Encephalopathy	<i>CDKL5</i> gene testing
Autosomal-dominant nocturnal frontal lobe epilepsy	Early childhood focal seizures in non-rapid eye movement (REM) sleep Lifelong seizures with spontaneous remissions and relapses	<i>CHRNA4</i> , <i>CHRN2</i> , <i>CHRNA2</i> gene testing
Etiologies of intractable epilepsy for which surgical therapy may be considered a treatment of choice ⁵⁴		
<ul style="list-style-type: none"> • Sturge-Weber syndrome • Hemimegalencephaly • Rasmussen encephalitis 	Low-grade cortical tumors Hippocampal sclerosis Focal cortical dysplasia	

Historical Features That Predict Evolution to Intractable Epilepsy

- History of multiple seizure types^{49,50}
- History of infantile spasms^{50,51}
- Onset of seizures in infancy^{52,53}
- Remote symptomatic etiology^{51,52}
- Abnormal neurologic examination^{50,53}
- Frequent seizures (daily or weekly) before treatment^{50,52}
- Early recurrence of seizures (within 6 to 12 months of treatment)⁵⁰
- History of status epilepticus before diagnosis^{49–51}
- History of neonatal seizures^{49,51}
- Mental retardation⁴⁹
- Seizure clustering⁵³

71.2 Components of a Surgical Evaluation

Once intractable epilepsy has been diagnosed, the focus turns to determining an etiology, locating the source of the seizures, and evaluating the treatment options. A surgical evaluation is frequently undertaken, especially in patients with focal-onset seizures of symptomatic or cryptogenic etiology, for whom an excisional procedure may provide a cure. Even for patients unlikely to be cured, such as those with multifocal epilepsy, symptomatic or cryptogenic generalized epilepsy, or mixed seizure

disorders, surgery may provide palliation, with efficacy equal or superior to that of alternative therapies.

The presurgical assessment should take place in a pediatric epilepsy center specializing in the evaluation of intractable epilepsy because the process is complex, and a team approach is required to develop successful treatment strategies. Every surgical evaluation must begin with a detailed description of each seizure type the patient has experienced because ictal semiology typically provides important localizing information (► Table 71.2). The ictal semiologies encountered in children are unique in that features may evolve throughout early childhood as the brain develops. In infancy, complex behavioral changes and stereotyped motor manifestations are less frequently encountered, likely because of immature neuronal networks.⁵ Typical lateralizing features of adult epilepsy (i.e., head version) are of less value in infants; the automatisms of infants are more often characterized by chewing or sucking, unlike the more stereotyped behavioral manifestations observed in older children and adults.^{6–8}

Intrinsic cerebral networks that inhibit seizure propagation develop over the first decade of life, at which time the typical lateralizing patterns of adult epilepsy begin to emerge. When patients are being evaluated for palliative surgical procedures, it is important to understand the frequency for each seizure type and the impact of the seizure type on quality of life. For example, while atypical absence seizures may be the most frequent seizure type in patients with Lennox-Gastaut syndrome, it is atonic seizures that lead to significant craniofacial injury and for which surgical treatment is often efficacious.

Table 71.2 Lateralizing and localizing seizure semiologies

Semiologic pattern	Commonly associated lateralization/localization
Auras	
Psychic (emotion, déjà vu)	Temporal lobe, limbic system
Nausea	Insular cortex, frontal operculum, mesial temporal lobe
Olfactory, gustatory sensations	Limbic system, olfactory bulb, insular cortex
Ictal features	
Head version	Contralateral hemisphere, motor area anterior to precentral gyrus
Eye version	Contralateral hemisphere, frontal eye field
Unilateral clonus	Contralateral hemisphere, primary motor cortex
Homonymous positive visual phenomena	Contralateral primary visual cortex
Asymmetric tonic posturing (flexion of one upper extremity, extension of the other)	Supplementary motor cortex contralateral to extended upper extremity
Unilateral eye blinking	Ipsilateral hemisphere
Unilateral automatism	Ipsilateral mesial temporal lobe or contralateral temporal neocortex
Unilateral somatosensory paresthesias	Contralateral somatosensory cortex or supplementary sensory motor area
Postictal features	
Receptive aphasia/dysphasia	Temporal lobe, dominant hemisphere (Wernicke area)
Expressive aphasia/dysphasia	Inferior frontal gyrus, dominant hemisphere (Broca area)
Hemiparesis/hemiplegia	Contralateral hemisphere, motor cortex

Source: Foldvary-Schaefer N, Unnwongse K. Localizing and lateralizing features of auras and seizures. *Epilepsy Behav* 2011;20(2):160–166⁵⁵ and Loddenkemper T, Kotagal P. Lateralizing signs during seizures in focal epilepsy. *Epilepsy Behav* 2005;7(1):1–17.⁵⁶

Table 71.3 Characteristics and purpose of components used in the surgical evaluation of childhood-onset epilepsy

Modality	Spatial resolution	Temporal resolution	Contribution
Scalp electroencephalography (EEG)	Poor	Very good	Localization of seizure onset and interictal regions of irritability/dysfunction
Magnetic resonance (MR) imaging	Very good	Poor	Anatomical definition of epileptogenic lesions
Positron emission tomography (PET)	Good	Good	Localization of focal regions of hypometabolism corresponding to epileptogenic cortex
Single photon emission computed tomography (SPECT)	Good	Good	Localization of focal hyperperfusion corresponding to ictal onset
Magnetoencephalography (MEG)	Good	Very good	Localization of spike clusters with dipole maps, mapping of eloquent cortex
Functional magnetic resonance imaging (fMRI)	Good	Good	Mapping of eloquent cortex
Diffusion tensor imaging (DTI)	Good	Good	Mapping of white-matter tracts

A detailed EEG evaluation, preferably with video, provides the foundation for most surgical evaluations. Children with a well-localized unilateral ictal onset more often attain seizure freedom, especially in cases with concordant interictal discharges and a recognized cerebral lesion on anatomical or functional imaging.⁹ Although patients may present with apparently generalized or multifocal EEG patterns, correlation

with detailed anatomical magnetic resonance (MR) imaging and multiple functional imaging modalities may reveal a localized onset.¹⁰ Several anatomical and functional studies are often required in an epilepsy evaluation, each with inherent strengths and weaknesses with regard to the spatial and temporal localization of ictal onset and functional cortex (► Table 71.3).

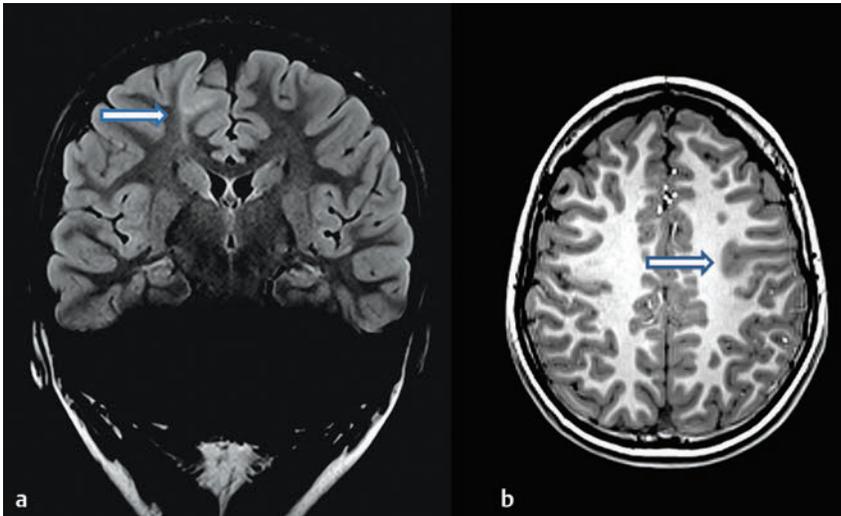


Fig. 71.1 Comparison of anatomical imaging characteristics of focal cortical dysplasia. (a) Example of transmantle sign (*arrow*) often encountered in type 2B cortical dysplasia (1.5 T [tesla], TR [repetition time] 9000, TE [echo time] 94, 3-mm slice thickness). (b) Example of cortical thickening and blurring of gray–white interface (*arrow*) seen in cortical dysplasia (3 T, TR 2100, TE 2.93, 1-mm slice thickness).

Anatomical high-resolution MR imaging with thin-slice volumetric T1-weighted gradient-recalled echo, in addition to axial and coronal T2, fluid-attenuated inversion recovery (FLAIR), and high-resolution T2 coronal imaging of the hippocampus provides excellent spatial localization of epileptogenic cortex and a basis for co-registering other imaging modalities. The most commonly encountered etiology of intractable focal epilepsy in children is focal cortical dysplasia, reported in more than 50% of cases in pediatric surgical series.^{11,12} Features of focal cortical dysplasia on MR imaging include focal cortical thickening, blurring of the gray–white junction, and increased gray matter signal on T2 or FLAIR imaging. The transmantle sign, characterized by a hyperintense white matter streak extending radially from the cortex to the lateral ventricle, may be encountered in higher-grade focal cortical dysplasia^{13–15} (► Fig. 71.1). Some of these features are more clearly delineated with post-processing techniques, such as voxel-based morphometry. The addition of 3-tesla MR imaging improves anatomical definition and will identify lesions in 65% of patients with previously reported negative findings on MR imaging.¹⁶ Difficulties may arise, however, when the substrate for epileptogenesis has a very subtle or no abnormality on MR imaging, as may occur in cryptogenic or nonlesional epilepsy. It is increasingly recognized that successful anatomical localization depends on multimodal analysis with the co-registration of other modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT).¹³ Co-registration techniques may even identify epileptogenic zones beyond those identified with MR imaging, as has been demonstrated with PET and magnetoencephalography (MEG).^{17,18}

SPECT relies on cerebral blood flow, which is focally increased during a seizure and may be decreased during the interictal period. Ictal and interictal studies can be compared with direct visual analysis, although the ability of SPECT to identify the epileptogenic zone increases with postprocessing techniques, such as subtraction imaging co-registered to the MRI.¹⁹ SPECT is limited by the requirement for an early ictal radiotracer injection, but it has proved especially useful in children with a poorly defined ictal onset, multifocal cortical abnormalities on anatomical imaging, and pseudo-generalized EEG patterns.

PET is a functional imaging modality based on cortical metabolism. Focal cortical hypometabolism can identify abnormal cortex and is especially useful in patients with nonlesional extratemporal lobe epilepsy and generalized EEG patterns.²⁰ PET is performed in the interictal state, which makes it logistically easier to complete. Because the focal region of abnormality identified by PET can both underestimate and overestimate the epileptogenic zone, data should be interpreted in the context of additional studies.²¹ Postprocessing techniques, such as statistical parametric mapping, in which the patient's PET is compared with a normative PET data set to identify regions of statistically significant hypometabolism, may provide additional value.²² PET is most frequently performed with an [¹⁸F]fluorodeoxyglucose ligand, although additional ligands, such as [¹¹C]flumazenil, which binds to the γ -aminobutyric acid A receptor, and α -[¹¹C]methyl-L-tryptophan (AMT), are also used. AMT may be particularly useful when multiple potentially epileptogenic foci are present, as may occur in tuberous sclerosis.²³

MEG is increasingly being used as a diagnostic component in the evaluation of intractable epilepsy and is best regarded as complementary to EEG. Whereas EEG relies on electrical potentials, which are altered by intervening tissue such as dura, cerebrospinal fluid (CSF), and bone, to localize epileptogenic cortex, MEG relies on magnetic fields, which are unaffected. This allows a more precise localization of horizontal spike generators, with a spatial localization of 3 to 4 cm², compared with 6 to 20 cm² for EEG.^{24,25} To detect a magnetic field, the electrical current must be parallel to the skull surface; thus, MEG detects tangential dipoles well, but radial dipoles are either attenuated or invisible. MEG becomes less sensitive as the distance from the source increases, so that deep foci (i.e., mesial temporal) may not be as well localized as superficial neocortical foci.²⁶ MEG can identify interictal spikes in patients with a normal EEG and may provide important localizing information beyond that of other presurgical modalities in up to 24% of cases.^{27,28} MEG-based magnetic source imaging can also be used to map eloquent cortex with paradigms to localize sensorimotor, visual, and verbal function. MEG is currently available in only a small number of epilepsy centers in the United States, which limits its use in most presurgical evaluations. MEG requires specialized

expertise for data analysis, and as with all functional imaging modalities, the quality of the final result is largely related to the experience of the center performing the test. The utility of MEG, like that of other new technologies, will likely evolve as the standardization of data acquisition and analysis improves.

Although localization of the epileptogenic zone is of the utmost importance to the success of epilepsy surgery, it is equally important to localize the relationship of eloquent cortex to the epileptogenic zone to avoid postoperative deficits. Functional MR imaging (fMRI), commonly used to localize eloquent cortex, detects changes in regional blood flow to map function. Paradigms for mapping sensorimotor, language, and vision function can be applied successfully in children as young as 5 years of age.^{29,30} These data complement presurgical localization of the epileptogenic zone to guide subdural electrode placement. With increasing recognition of the accuracy of fMRI, the intracarotid amobarbital (Wada) procedure is rarely employed at most centers.

Additional imaging techniques, such as diffusion tensor imaging (DTI), provide important information regarding the functional connectivity of eloquent cortex, which is essential to surgical planning. The flow of water molecules along nerve fibers is restricted in the perpendicular plane (i.e., anisotropic), whereas the flow of CSF is unrestricted (i.e., isotropic). DTI uses this anisotropy to visualize white matter tracts, which can then be co-registered in multimodal analysis so that their relationship to the epileptogenic zone can be understood. DTI has anatomical accuracy comparable with that of subcortical mapping, and the presurgical appearance of DTI tracts may be useful in

predicting postsurgical deficits, with patients demonstrating displaced tracts experiencing less deficit than those in whom the tracts are included in the target lesion.³¹⁻³⁴

The individual imaging components included in a child's evaluation are dictated by the clinical circumstances of the epilepsy. For example, patients who have single well-defined cortical lesions concordant with EEG data may not require SPECT or PET but may benefit from fMRI if the lesion is in close proximity to eloquent cortex; in contrast, patients with apparently normal MR imaging findings or a poorly localized scalp EEG often benefit from PET, SPECT, or MEG to better define the region of abnormal cortex. It is generally accepted that multimodal analysis with co-registered imaging data improves localization, surgical planning (i.e., grid placement), and ultimately surgical outcome. Studies of the co-registration of MR imaging with SPECT and MR spectroscopy data demonstrate a sensitivity of 100% for focus lateralization in temporal lobe cases and particular localizing efficacy in patients with negative MR imaging results.³⁵ Similarly, PET co-registered with MR imaging may significantly improve the yield of focus localization compared with PET alone and may be especially valuable for patients with low-grade cortical dysplasia or discordant data, improving the postsurgical outcome.^{18,36,37}

To perform multimodal analysis, noninvasive presurgical imaging should be obtained in a resolution that permits three-dimensional or orthogonal representation, which in turn allows the co-registration and scaling of data. The volumetric T1 MR image most often serves as the anatomical reference image for the co-registration of all other modalities. Once imaging data

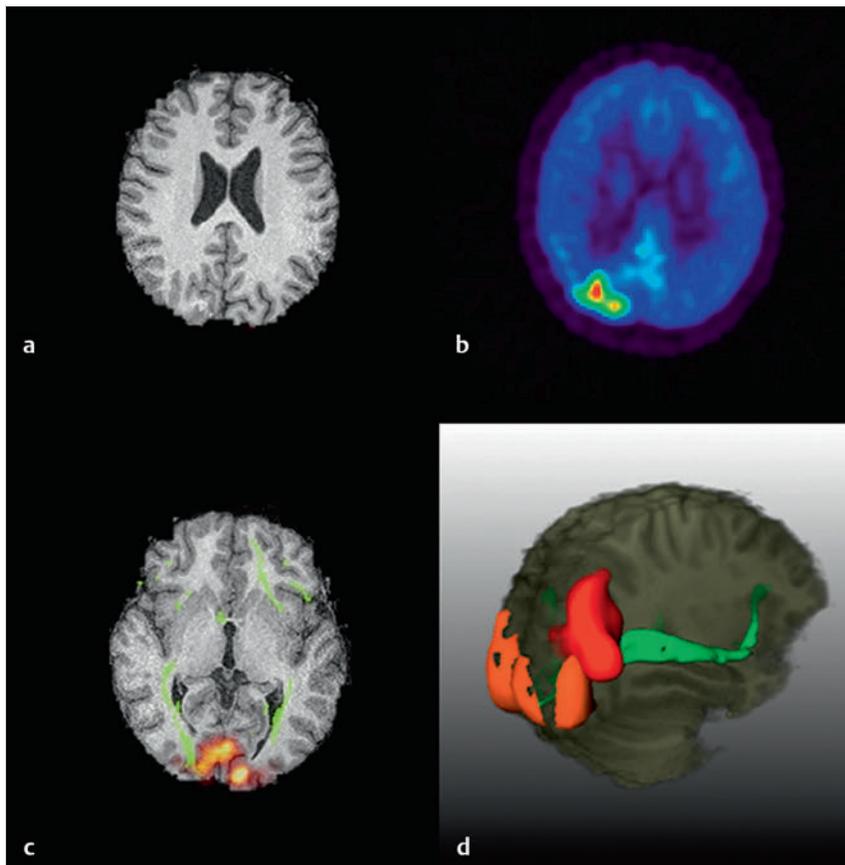


Fig. 71.2 Multimodal imaging analysis with co-registered presurgical imaging data. (a) Two-dimensional magnetic resonance (MR) imaging. (b) Positron emission tomography (PET) performed during focal status epilepticus with ictal hypermetabolism (red). (c) Functional MR imaging/diffusion tensor imaging (fMRI/DTI) with visual cortex (orange) and overlying visual tracts (green). (d) Co-registration with three-dimensional MR imaging representation and overlay of fMRI (orange), PET (red), and DTI (green).

are co-registered, a number of postprocessing techniques can be used to create overlays of each modality, providing an excellent representation of epileptogenic zone localization, grid placement, and the functional connectivity of eloquent cortex (► Fig. 71.2).

71.3 Predictors of Seizure Outcome

Once the presurgical evaluation is complete, the patient's data must be reviewed to determine candidacy for epilepsy surgery. This discussion often involves multiple medical specialists, including epileptologists, neurosurgeons, neuropsychologists, and neuroradiologists. The primary goal is to determine the likelihood that surgery will result in seizure freedom or significant seizure reduction such that the benefits of surgery outweigh the risks of the procedure. Patients referred for surgical therapy may undergo single-stage procedures for well-localized ictal onset or multiple-stage procedures in which chronic subdural or depth EEG is employed. Patients who undergo multiple-stage procedures generally have an inadequately defined epileptogenic zone or a zone of seizure onset that is in close approximation to eloquent cortex and requires more precise subdural cortical mapping.

Numerous pre-, peri-, and postoperative variables contribute to the successful outcome of epilepsy surgery, and all must be carefully considered when patients and their families are counseled regarding treatment options. Of the multiple variables that contribute to success, the most important is completeness of the epileptogenic zone resection.^{38,39} In a series of pediatric patients who had focal cortical dysplasia, 70% with complete resection remained seizure-free, versus only 22% with incomplete resection.³⁸ The definition of the epileptogenic zone continues to evolve but relies heavily on the anatomical lesion defined by MR imaging and the physiologic lesion defined by electrophysiology. Each contributes significantly, and neither alone defines the epileptogenic zone, as patients with complete resection of both the anatomic and the physiologic epileptogenic zone have a better outcome than do those with complete resection of only one of the zones.⁴⁰ In many cases, the zone of seizure onset may extend beyond the borders of the lesion evident on MR imaging; this situation is often encountered in patients with low-grade cortical dysplasias or developmental tumors bordered by dysplastic cortex. In such circumstances, complementary imaging modalities such as MEG and PET may better define the borders of the epileptogenic cortex.^{17,18}

Further definition of the physiologic epileptogenic zone relies on subdural electrophysiologic data, obtained with either intraoperative electrocorticography or prolonged extraoperative subdural encephalography. For both, accurate presurgical localization is necessary to ensure proper electrode placement. Internally, the epileptogenic zone is characterized by regions of active spiking with constant focality, focal regions of rhythmic fast activity, and associated focal attenuation of the background.^{38,39} Patients undergoing extraoperative subdural monitoring are further characterized with ictal data. Several other variables contribute to seizure-free outcome after epilepsy surgery, with many ultimately related to the completeness of resection (see box "Predictors of Seizure-Free Outcome following the Surgical Treatment of Intractable Childhood-Onset Epilepsy (p.937)").

Predictors of Seizure-Free Outcome following the Surgical Treatment of Intractable Childhood-Onset Epilepsy

- Preoperative variables
 - Older age at seizure onset⁴¹
 - Unifocal lesions on MR imaging^{40,41}
 - Psychiatric comorbidities^{57,58}
 - IQ > 70⁵⁹
- Operative variables
 - Completeness of resection^{38,39,60,61}
 - Unilobar resection^{12,40,41}
 - Temporal lobe resection^{12,41,62}
- Postoperative variables
 - Histopathology (tumor > cortical dysplasia)^{12,41}

There are some situations in which patients may be less likely to achieve seizure freedom following surgical therapy, yet they still deserve further consideration. For example, patients in whom presurgical evaluation suggests that resection of the epileptogenic zone will be incomplete, such as those with an onset zone encroaching on eloquent cortex, may still achieve seizure freedom. In a series of patients with incomplete resections, 40% achieved seizure freedom; those who had complete resection on either MR imaging or EEG were more likely to remain seizure-free than those with complete resection on neither MR imaging nor EEG.⁴⁰

Another commonly encountered circumstance is the requirement for multilobar resections, seen in 12 to 22% of pediatric series.^{41,42} Although outcome is more favorable after unilobar procedures, more than 40% of appropriately chosen patients undergoing multilobar resections remain seizure-free at 10 years postoperatively, with those undergoing extended posterior or quadrant resections faring best.⁴³ This is further discussed in Chapter 72.

For some patients, the expected surgical outcome is not seizure freedom but palliation of the most dangerous or frequent seizure type. For example, corpus callosotomy is often employed to treat atonic seizures associated with Lennox-Gastaut syndrome, which pose considerable medical risk related to fall and injury. Even in patients clearly demonstrating a multifocal ictal onset, resection of the region associated with the most debilitating seizure type can still prove beneficial.⁴⁴ For others, such as those with epileptic encephalopathies, surgical intervention may serve to prevent further cognitive decline as well as reduce seizures. Surgical therapy has been used successfully to treat Ohtahara syndrome, West syndrome, and Landau-Kleffner syndrome, achieving improvement in cognitive development in addition to seizure reduction.⁴⁵⁻⁴⁸ In all palliative cases, the goal of surgical therapy must be clearly delineated a priori in order to objectively assess the success of the procedure.

The evaluation of medically intractable childhood-onset epilepsy is a complex endeavor that requires a thorough understanding of pediatric epilepsy and the etiologies that lead to intractability. Well-performed evaluations not only localize ictal onset, but also help delineate cause, such that the recommended treatment matches the underlying etiology. Surgical therapy is an increasingly viable approach to treating intractable epilepsy,

with the spectrum of patients considered candidates steadily increasing, although surgery remains an underutilized treatment strategy. There are a number of features that predict treatment failure early on in medical therapy, and clinicians should maintain a low threshold for undertaking a more extensive evaluation as the epilepsy of these patients becomes intractable.

Pearls

- Medically intractable epilepsy is defined as the failure of two adequate trials of appropriately chosen and tolerated AEDs to achieve seizure freedom.
- Pseudo-intractability is an important concept that must be explored through careful evaluation before more extensive surgical evaluations are undertaken.
- Patients who have localization-related epilepsy with a well-defined ictal onset are excellent candidates for surgical evaluation and potential cure. However, patients with multifocal localization-related epilepsy, a symptomatic generalized epilepsy, or an ictal onset for which complete resection is not possible may still benefit from surgical therapy.
- The presurgical evaluation of intractable epilepsy requires a detailed history, neurophysiologic data, and a number of anatomical and functional imaging studies to accurately define the ictal onset zone.
- Several pre-, peri-, and postoperative variables contribute to the likelihood of seizure freedom following surgical therapy for intractable epilepsy, although none are as important to outcome as completeness of the epileptogenic zone resection.

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72 Temporal Lobe Epilepsy

Jeffrey Ojemann

Epilepsy is defined as recurrent, unprovoked seizures and is present in up to 0.5 to 1% of the population.^{1,2} The incidence of epilepsy is age-dependent, with approximately 50 or so new pediatric cases diagnosed per 100,000 per year.²⁻⁵ In up to one-third of young patients, epilepsy becomes intractable,⁶ and the majority of seizures remain of unknown origin. Nevertheless, a significant portion of the seizures do have a temporal lobe onset, and these patients are candidates for surgical treatment with the resection of temporal lobe foci. Up to 10% of cases of new-onset childhood epilepsy may have lesions,⁷ many in the temporal lobe. Most temporal lobe seizures are of unclear etiology, although genetic syndromes have been described.⁸ This chapter focuses on the evaluation and surgical management of this population.

Temporal lobectomy is the only surgery with level 1 evidence to support its use⁹ in an adult population. There is no such equivalent study for children. The evidence is very strong to support that surgical outcomes are more favorable than the natural history,¹⁰⁻²³ and in fact, a randomized study in children would likely not be undertaken, given the strength of current data.²⁴

Most cases of epilepsy are treated successfully with medication. A single agent can control epilepsy in the majority of patients.^{5,25} However, once the first agent has failed, successive drugs or combinations of drugs have a rapidly diminishing rate of success. After two failed drugs, the chance of complete seizure freedom with any medical combination is poor.^{5,25} The rate of intractability in patients with lesions and new-onset seizures has been much higher than in patients without lesions.^{6,7,26} In fact, the majority of those presenting with lesions do ultimately have recurrent seizures when followed for many years. Thus, early surgery should be strongly considered for children with difficult-to-control seizures and a lesion congruent with other evaluations.

72.1 Temporal Lobe Seizures: Semiology and Electroencephalographic Findings

Most temporal lobe seizures are complex partial seizures.²⁷ The characteristic temporal lobe seizure semiology in adolescents may be similar to that in adults. Epigastric rising, ictal vomiting (especially on the nondominant side), and experiential feelings (déjà vu, an abnormal feeling of familiarity; jamais vu, a lack of familiarity with an item that should be familiar; other feelings of altered time or flow of time) may resemble adult semiology. Speech alterations are common postictally after seizures in the dominant temporal lobe. The memory of temporal lobe seizures and surrounding events can be impaired. The recollection of seizure frequency may be an underestimate, especially if caregivers are not always present to witness any seizures.

In infants and young children, the semiology may be quite different. Hypomotor, motor, and epileptic spasms may all be seen.^{2,28,29} Dystonic posturing begins to be seen in young children.² Apnea can be the presenting form of temporal lobe epilepsy in the very young.^{30,31}

72.2 Natural History

Before the widespread use of surgical intervention, the natural history of poorly treated temporal lobe epilepsy was documented.^{32,33} Ongoing seizures can lead to a poor neurocognitive, behavioral, and psychosocial outcome.³⁴ A lack of seizure freedom, unemployment, and dependence, all contributing to social isolation, are common long-term findings.

The negative impact on cognitive function can be multifactorial. All antiepileptic drugs have side effects and, even at therapeutic levels, can adversely affect cognitive and behavioral function in children.³⁵ Even newer drugs, which may be better tolerated, have clear side effects. Levetiracetam is associated with behavioral disturbances and topiramate with language deficits, for example. Seizures may exist in association (causal or otherwise) with an underlying brain disorder. These disorders may primarily drive cognitive dysfunction. Lower measures of intelligence³⁶ and behavioral, schooling, and learning difficulties^{33,37} are all seen in this population, with adverse effects on quality of life.³⁸

Mortality is increased in children with uncontrolled epilepsy,³⁹ although the underlying neurologic disorder may contribute significantly to this finding.²

72.3 Evaluation

Diagnostic electroencephalography (EEG) is typically performed in the evaluation of children suspected to have epilepsy. Routine EEG can be normal in up to 50% of patients with epilepsy⁴⁰ thus, a single negative study does not exclude the diagnosis. Similarly, in a patient who clearly has temporal lobe epilepsy, a routine EEG may be normal, especially if the seizures are rare. However, a longer-term EEG, such as video EEG, which captures longer periods of time and ideally specific events, is typically sought as part of the evaluation. In temporal lobe epilepsy, anterior temporal interictal discharges are common. In fact, the absence of interictal discharges calls into question the diagnosis of medial temporal lobe seizures. The presence of lateralized interictal spikes is quite significant in the localization of seizures to one temporal lobe.

Auras may not have EEG changes, but full seizures would be expected to show EEG changes. Typical changes may include anterior temporal lobe spike-wave complexes, focal temporal lobe slowing, and temporal intermittent rhythmic delta activity (TIRDA). These may have a tendency in younger children to appear less focal.² Ictal recordings may rapidly spread and appear bilateral or even generalized.²

Magnetic resonance (MR) imaging arguably provides the most important piece of information in determining candidacy for temporal lobectomy.⁴¹ As in adults, hippocampal signal change, including hippocampal sclerosis, may be identified (► Fig. 72.1). However, the findings may be more subtle than in adults, and MR imaging findings may be absent in many cases, even cases of histologically proven sclerosis.¹⁴ More importantly, other pathologies are prevalent in pediatric series, including dysplasia of the hippocampus, parahippocampus, and/

or anterior temporal cortex. The concept of dual pathology is critical to pediatric epilepsy surgery. The presence of *both* a neocortical *and* a medial temporal lobe pathology is well described (► Fig. 72.2).^{15,42–45} Although the exact mechanism is

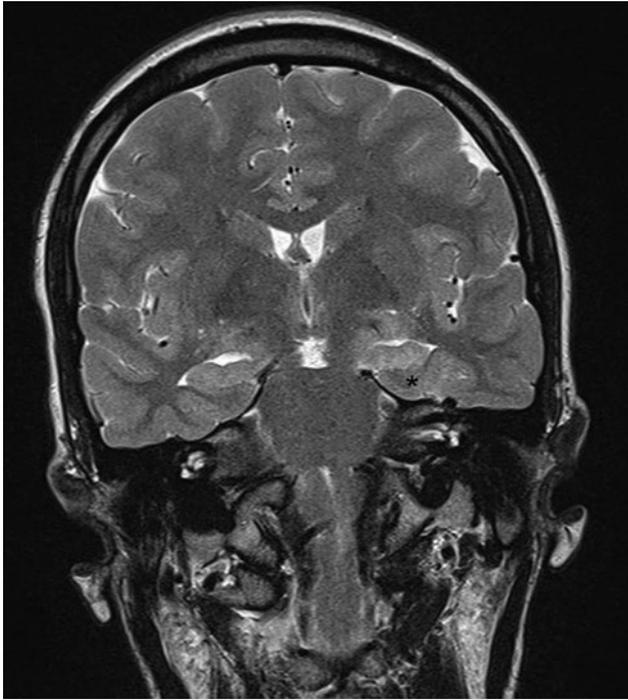


Fig. 72.1 Coronal T2-weighted magnetic resonance image showing left hippocampal sclerosis in a 3-year-old. The hippocampus (*) is small, with increased signal and absence of the internal architecture (see the dentate gyrus on the normal, right side).

unknown, the development of hippocampal pathology is presumed to be secondary to the primary lesion, becoming a second focus. Alternatively, the medial temporal changes can be part of the same underlying process(es), especially in the case of abnormalities (e.g., dysplasia) of the adjacent temporal lobe neocortex (► Fig. 72.3).

As in adults, MR imaging signal changes on the T2 and FLAIR (fluid-attenuated inversion recovery) sequences can help establish the diagnosis. However, volume loss may be less common. In fact, a dysplastic hippocampus can look thickened on coronal imaging, along with a fattened amygdala. Loss of the internal architecture of the hippocampus is seen in many cases, including those in which the hippocampus does not have volume loss (► Fig. 72.4). Other subtleties, such as abnormal organization of the basal temporal gyri,⁴⁶ may be best seen on three-dimensional reconstructions, some of which are not part of widely available imaging software packages. However, hippocampal sclerosis may be difficult to detect, and MR imaging may be normal in up to one-half of cases.¹⁴ Nevertheless, surgery for patients with negative MR results may still be successful.⁴⁷

Other MR imaging findings that can argue for epilepsy surgery are medial or lateral temporal lobe tumors⁴⁸ (► Fig. 72.5). These are typically low-grade tumors, such as gangliogliomas, dysembryoplastic neuroepithelial tumors (DNETs), or pilocytic tumors; however, malignant tumors, especially supratentorial primitive neuroectodermal tumors (PNETs), can present with seizures in the medial temporal lobe.

In the case of tumors, it may be advisable to proceed with surgery for oncologic reasons as well as for epilepsy control.⁴⁹ Although a benign-appearing lesion may not grow for some time, the epileptogenic nature of such a lesion can be established much more quickly than in nonlesional cases.²⁶ Given the frequent progression to intractability and the better prognosis

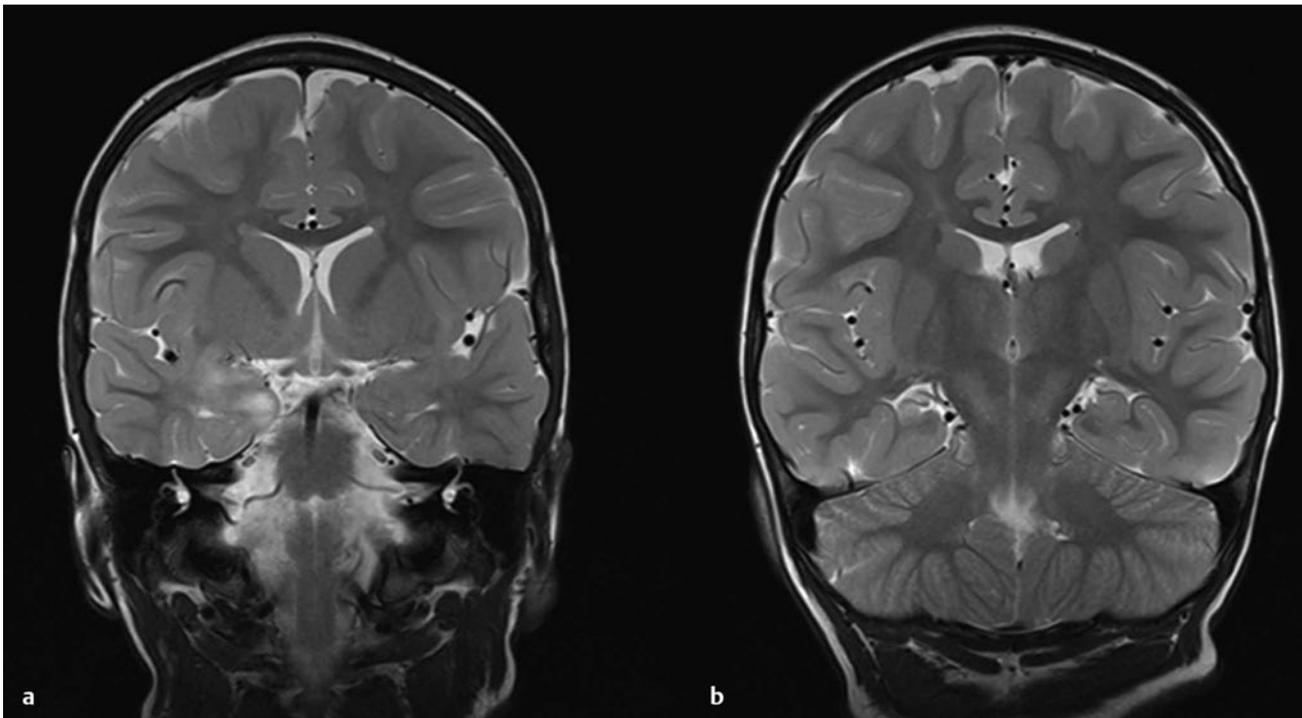


Fig. 72.2 (a) Lesion of the amygdala. (b) Hippocampal sclerosis co-presenting with the lesion in (a).

with surgery, resection of a tumor is typically indicated, just as a headache-causing tumor, even if likely benign, would typically be removed. Furthermore, resection allows a more accurate diagnosis by limiting the risk for undersampling. In the case of more aggressive lesions (► Fig. 72.6), early diagnosis and gross total resection may increase survival.

In the case of normal MR imaging findings or of EEG and MR imaging data that are not congruent, other imaging modalities may be employed.⁵⁰ Positron emission tomography (PET) with fluorodeoxyglucose (FDG) allows an assessment of the metabolic status of the cortex and can reveal temporal lobe foci.^{51,52} Epileptic foci are typically hypometabolic during the interictal phase (► Fig. 72.7). After a morning fast, radioactively la-

beled FDG is injected over 45 minutes. Cortical uptake allows measurement of the regional glucose metabolism. The period during injection should be quiet, without sensory stimulation or significant spontaneous movement; otherwise, those parts of the brain involved in, say, vision, somatosensory experience, or movement will show increased activation. During seizures, or even frequent interictal discharges, the local regional metabolism may increase. This can give a mixed picture, and the interpretation is often helped by recording the EEG during the PET to assess the interictal versus the ictal state.

Typically, the interpretation is made by comparing the two hemispheres and commenting on relative hypometabolism on one side. Statistical parametric maps can compare glucose metabolism (normalized to overall brain metabolism) with a database of PET scans from persons without epilepsy. This may better identify foci. The lack of large databases of pediatric PET scans has limited this approach, however.

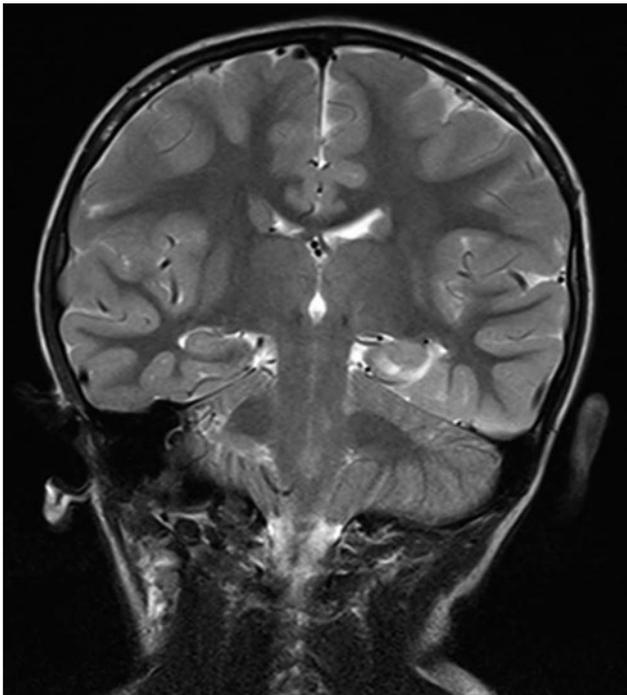


Fig. 72.3 Dysplastic lesion involving the parahippocampus and hippocampus on the left side.

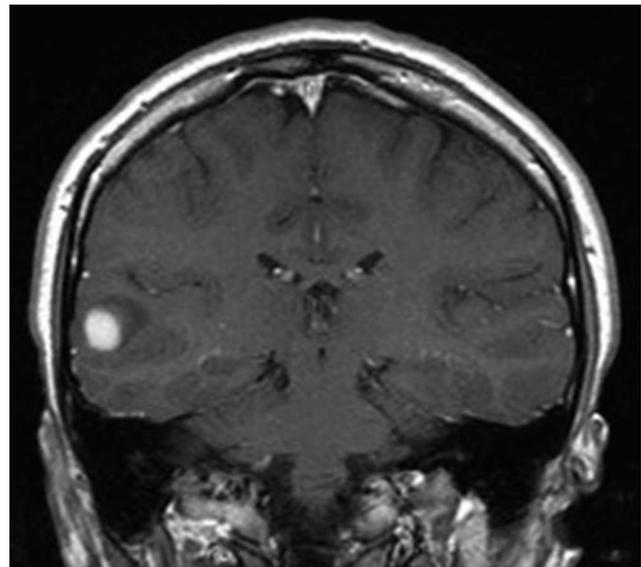


Fig. 72.5 Lateral temporal lobe lesion presenting with epilepsy. Resection showed a pilocytic astrocytoma.

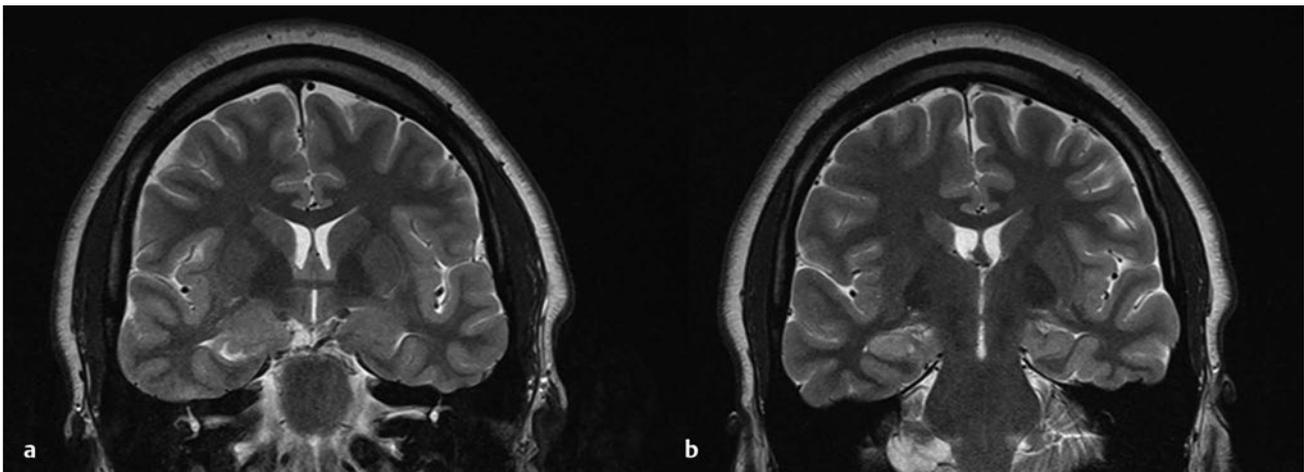


Fig. 72.4 (a) Anterior hippocampus and amygdala showing dysplastic lesion. (b) Extension of the abnormality into the hippocampus, with thickening of the hippocampus and loss of normal internal architecture.

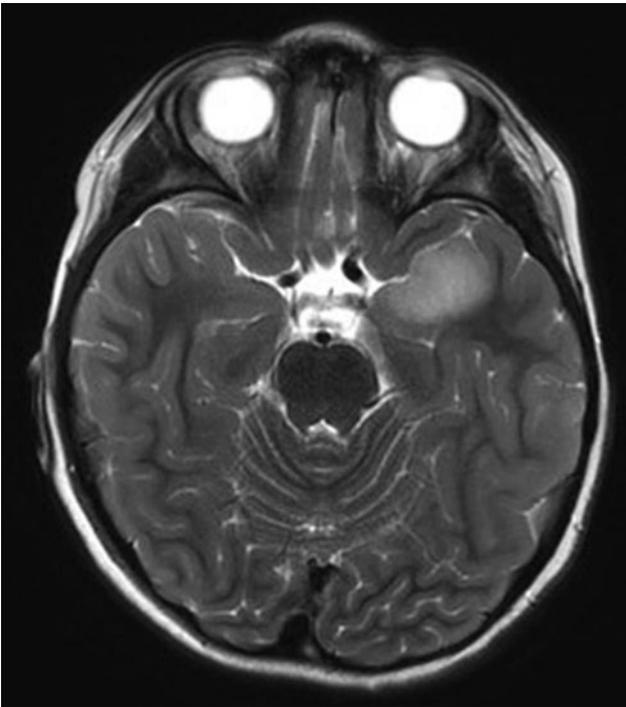


Fig. 72.6 Axial T2-weighted magnetic resonance image. Although it was not enhancing and presented with some hippocampal signal change, the lesion was malignant, a primitive neuroectodermal tumor.

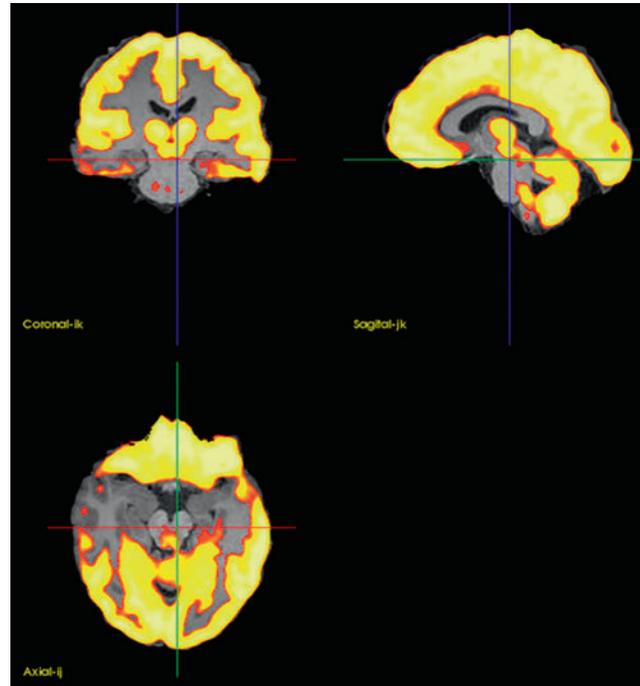


Fig. 72.7 The medial temporal hypometabolism on the positron emission tomographic (PET) scan (color scale) is superimposed on the magnetic resonance image. This co-registration aids in localization of the abnormality.

Single photon emission tomography (SPECT) studies⁵³ are obtained by injecting during the beginning of a seizure and during the interictal phase. This is typically done on the telemetry floor, so that the onset of a seizure can be determined both by the early clinical manifestations and/or by early changes in the EEG if it is being monitored by a knowledgeable technician. Then, the injection must be performed quickly to maintain the ability to obtain a valid localization. Because the logistical requirements (e.g., radiation handling, need for an EEG technician, qualifications of the technician, bedside nursing needs) are significant, these studies are done mostly at larger centers and/or are reserved for more challenging localization situations.

Subtraction of the ictal and interictal studies can show the blood flow change associated with seizure onset. The onset zone will show increased blood flow relative to the interictal baseline. The method is quite sensitive to late injection, early spread, and other factors that may lead to incorrect localization.

Other modalities that are employed less often⁵⁰ include magnetoencephalography (MEG), high-density EEG, and MR spectroscopy. MEG measures the magnetic field of brain activity and may help localize temporal lobe interictal activity.⁵⁴⁻⁵⁶ Movement is poorly tolerated, and primarily interictal studies are recorded. High-density EEG involves the placement of up to 256 electrodes to improve spatial sampling and may provide additional information.⁵⁷ Other sophisticated EEG mapping tools hold promise in increasing localization power.⁵⁸ Other MR imaging methods, such as MR spectroscopy, which looks at the chemical composition of the temporal lobe,⁵⁹ and functional connectivity MR imaging,⁶⁰ which looks at cross-region interactions, are emerging technologies that show promise in the diagnosis of temporal lobe epilepsy.

The extent of resection, and certainly the preoperative consultation, will be influenced by whether surgery is to be performed on the dominant or nondominant temporal lobe. Dominance is typically in reference to language function. Historically, dominance was established by the cerebral Amytal (or Wada) test. In this test, each hemisphere is independently injected. A short-acting anesthetic, such as amobarbital (Amytal; Marathon Pharmaceuticals, Deerfield, IL) or an alternative, is administered through a selective carotid artery injection. The injected hemisphere is temporarily disabled. Injection into the dominant hemisphere characteristically leads to the inability to speak. Memory dominance is indicated by the inability to remember items presented during the hemispheric anesthesia.⁶¹ The test is limited by the distribution of anesthetic, which does not well cover the hippocampus or posterior-medial temporal lobe, although it does cover frontal as well as temporal areas. Left dominance is extremely common in right-handed individuals with a normal developmental history.⁶² Functional MR imaging has increasingly been used as an alternative mechanism to establish dominance.⁶³⁻⁶⁵ Furthermore, it is suspected that children can better tolerate resection of the dominant temporal lobe; however, the evidence for this is minimal, and verbal memory deficits can be seen,⁶⁶ as in adults.⁶⁷ Functional MR imaging (and the Wada test) require a cooperative patient and can, by a person with significant training, be done in children as young as 5 years of age.^{68,69}

Surgical resection is often guided both by the preoperative evaluation, including imaging, and also by direct brain recordings, or electrocorticography (ECoG). ECoG can be acquired intraoperatively⁷⁰⁻⁷³ or over longer periods by implanting electrodes for several days.⁷⁴ The latter approach is used when diagnostic localization is unclear despite noninvasive tests (► Fig. 72.8). Typically,



Fig. 72.8 Dual pathology on invasive monitoring. Independent interictal discharges are seen in basal temporal electrodes (rows RAT3, RAT4, and RAT5 [*]) and in medial temporal structures (RMT1 [†]).

the questions relate to the extent of medial versus lateral involvement in temporal lobe epilepsy (beyond what can be addressed in a standard resection), the evaluation of orbitofrontal and/or insular involvement, the inclusion of the temporal lobe in a case in which multiple regions may be involved based on evaluation, and the localization of function (e.g., speech) before a resection.⁷⁵

Intraoperative ECoG⁷⁶ is limited by the length of recording and is typically interictal, although a seizure may be fortuitously recorded, especially in an active case. There is no standard for duration, and the required length of time of recording may vary depending on the question at hand. If ECoG is being used to limit a resection, say, of the hippocampus,^{70,77} then frequent interictal activity in just a few minutes is sufficient to exclude the null hypothesis⁷⁸ and therefore justify resection of the involved area (provided the area was suspected to some degree ahead of surgery). The use of intraoperative ECoG to augment lesionectomy is a common strategy in temporal lobe surgery,⁷⁹ both to ensure adequate neocortical resection⁷⁹ and also to assess the role of the inclusion of medial temporal (e.g., hippocampal) structures. This approach is supported by meta-analyses that suggest superior outcomes⁸⁰ and other comparison studies,⁸¹ but a direct comparison has not been done, and lesionectomy alone may be a successful strategy in some cases.^{82,83} Intraoperative ECoG can be influenced by anesthetics⁸⁴ propofol (Diprivan; Pfizer, New York, NY), dexmedetomidine,⁸⁵ and sevoflurane are typically used, although minimization of anesthesia as tolerated during actual recordings may be indicated.

Implanted ECoG may use subdural grid and strip electrodes, depth electrodes, foramen ovale electrodes, or a combination of some or all of these configurations.^{74,86,87} Medial temporal lobe coverage should include the hippocampal and parahippocampal regions.⁸⁸ Electrode leads are tunneled through the scalp after the dura is closed and the bone flap reapproximated. Alternatives for closure include loose reapproximation of the bone flap, use of an osteoplastic flap, and sterile storage of the bone flap until removal of the electrodes and resection, as indicated by the results of the monitoring. Electrode placement is generally well tolerated but does carry a higher risk for infection compared with other surgeries, and neurological deficits, especially transient, can occur.^{89–91}

72.4 Surgical Approach: Lesionectomy

When a lesion has a benign appearance, such as of dysplasia, a cavernoma, or a hamartomatous lesion (e.g., DNET), then the

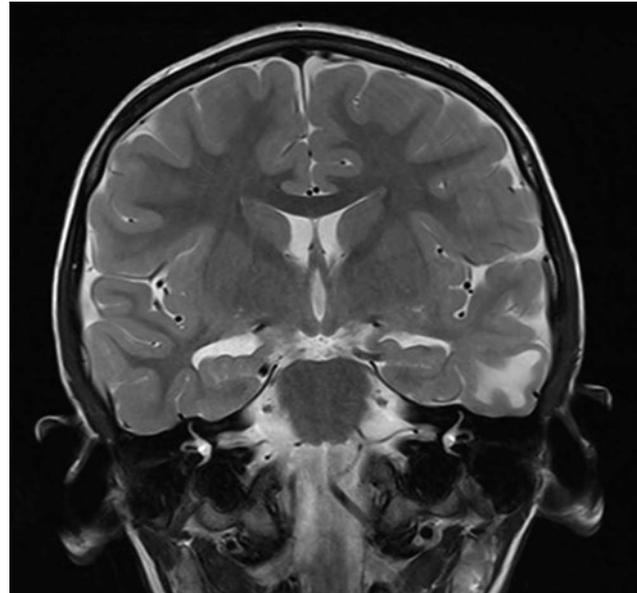


Fig. 72.9 Type IIB dysplasia of the lateral temporal lobe. The medial structures were spared, with seizure freedom on long-term follow-up.

decision to operate is usually driven by seizure control. EEG evidence of congruent interictal or ictal activity further supports surgery, but the absence of EEG abnormalities should not preclude surgery if other aspects of the evaluation (e.g., seizure type, neuropsychology) are congruent with the MR imaging appearance of the lesion. As discussed above, there is weak evidence to support the use of ECoG to enhance seizure resection. This is particularly true when adjacent structures are suspected, as in the case of hippocampal involvement in anterior–medial tumors.

The surgical steps of temporal lobe lesionectomy depend on whether the target is medial, lateral, or some combination thereof. Lateral lesions (► Fig. 72.9) are readily approached through a standard craniotomy. For many lesions, neuronavigation will be helpful in planning the incision and bone flap. Epidural hemostasis is achieved and a dural opening made in the usual fashion. Normal end-tidal CO₂ along with attention to head positioning is usually adequate. Cerebrospinal fluid aspiration can be used to achieve brain relaxation without the need for diuretics or hypoventilation. Elevation of the head is also unnecessary and increases the risk for air embolus. Steroids may be considered before surgery and may aid recovery.

Navigation may be especially important in cases of intrinsic brain tumors that may have a visual appearance similar to that

of normal cortex. Dysplastic tissue may be firm to gentle palpation and will aspirate differently from surrounding cortex; it often has a foamy appearance when the ultrasonic aspirator is used on lower settings. Dysplasia is particularly common in association with mesial temporal lobe pathology,^{42,45} although in an adult series, anterior gray-white abnormalities did not have to be completely resected.⁹² If EcoG is performed before lesion removal, the extent of resection can be planned.

Functional considerations often determine the practical limit of resection. Tissue that is disconnected or can be undermined by resection into the white matter of the temporal lobe need not be spared. However, resection into speech areas will increase morbidity. As discussed before, language dominance may be determined with cerebral amobarbital or imaging, but language dominance is often inferred by side and clinical presentation. Many dominant temporal lesions are well anterior and/or medial to suspected speech areas. However, for more lateral and posterior lesions, speech mapping may be necessary if the boundaries of a lesion are not distinct or approach language areas. Speech mapping can be performed with an awake surgery even in a preadolescent patient,⁸⁵ or invasive monitoring can be performed to determine language localization before a definitive resection. Speech may be different in children, with temporal lobe sites less common in one series.⁶³

On the nondominant side, resections of the lateral surface are not reliably associated with clinically obvious deficits. Thus, a major consideration is extensive resection of the basal temporal lobe that could lead posteriorly to impairments of face processing, although the anatomical correlation with clinically relevant deficits remains unclear. Visual field deficits will be limited to quadrantanopsia unless the resection is taken so far back that inferior field fibers are injured where they come out of the geniculate. Of note, these fibers can be injured with a far posterior-lateral temporal resection. The vascular supply coming off the depth of a lateral temporal-occipital sulcus can be a tenuous supply to geniculocalcarine radiations, and hemianopsia following posterior-lateral temporal resection can be seen.

Once the extent of resection is determined, the corticectomy can begin with coagulation of the pia. Dividing the pia sharply allows ultrasonic aspiration of the lesion. Many lesions will respect adjacent sulci, and the subpial approach⁹³ allows a nice delineation of the resection boundaries. If gyral vessels are inadequately coagulated, they may retract, and coagulation of the cut pial edge and deeper coagulation when a sulcus is approached is usually sufficient. The operative microscope aids in discerning lesion margins and preserving the tissue and vascularity of surrounding brain.

For lesions that are less superficial, the temporal horn of the lateral ventricle provides a critical landmark to avoid extension of the resection through the temporal stem or into the subcortical structures. Inferior and anterior to the ventricle, the medial pia is a reliable boundary between major vascular structures, the brainstem, and cranial nerves. Some pathologies will cause the pia-tissue interface to be more adherent; however, the plane can usually be identified at the edge of the tentorium and followed medially.

Above the ventricle, no such barrier exists, and resection must not violate the basal ganglia or perforators from the middle cerebral artery. Thus, for deeper lesions, identification of the lateral horn should be an early step. By taking the resection

anteriorly and inferiorly first, and then resecting superiorly and posteriorly at the same depth, it is guaranteed that one will enter the ventricle before violating the temporal stem. If the superior and posterior resections of temporal cortex are not kept as superficial as the anterior and inferior extent, this relationship is lost, and other means of keeping the resection safe will be required.

72.4.1 Medial Resections

The appropriate extent of surgery and the approach to medial regions are controversial.⁹⁴⁻⁹⁶ So-called "selective" approaches advocate minimal resection of the lateral cortex, "standard" temporal lobectomy with aggressive resection of the lateral temporal lobe cortex (classically 4 cm on the dominant side and 6 cm on the nondominant side), and "tailoring" with EcoG and sometimes functional (speech) considerations to determine the lateral extent. Although in adults selective procedures seem to be adequate,⁹⁷ several studies suggest that a highly selective approach in children will miss significant temporal lobe pathologies and should be used with caution.^{98,99}

The entry to the ventricle is the key first step in approaching medial temporal structures. Of the myriad of so-called selective approaches, all but the transylvian approach¹⁰⁰ require entry into the ventricle as part of the resection before removal of the medial temporal lobe. A standard temporal lobectomy involving resection of the lateral cortex can be limited to the middle temporal gyrus, often as little as 3 cm, and can be tailored based on the presence or absence of recorded epileptiform activity by EcoG or imaging or on other concerns for anterolateral temporal involvement. Because the ventricle typically sits under the superior temporal sulcus, extensive resection of the superior temporal gyrus is usually unnecessary solely for the purpose of reaching the ventricle. An approach through the middle temporal gyrus or through the inferior temporal gyrus or upward retraction and resection of the fusiform gyrus,¹⁰¹ will allow an approach to the ventricular wall. A more posterior approach can also be used.¹⁰² Once the ventricle is entered, the lateral amygdala, choroid, and hippocampus are typically visible, even in the setting of mass lesions. The ventricular wall can be opened along the extent of its exposure. Early in the process, a cotton patty can be placed in the ventricle to avoid bleeding into the remainder of the ventricular system. Additional EcoG can now be performed directly on the hippocampus. The lateral amygdala can be resected flush with the roof of the ventricle; however, there is no pia to provide a superior border. The mesial pia will be encountered from any of several maneuvers—resection of the lateral amygdala, superior extension of the resection of the basal temporal lobe, resection of the temporal lobe off the sylvian fissure anterior to the ventricle, and resection of the hippocampus anteriorly off the choroidal fissure. The order of these steps is arbitrary and can be modified according to the surgeon's preference.

If the superior temporal gyrus anterior to the ventricle is removed early in the resection, the sylvian fissure can be followed laterally to medially. With the use of operative microscopy, the resection is taken anteriorly to the middle cerebral artery, which can often be seen through the intact pia. As the resection is taken in the inferomedial direction, the mesial pia will be encountered. The lateral amygdala resection can be completed here as the most medial part is taken off the pia. At this point,

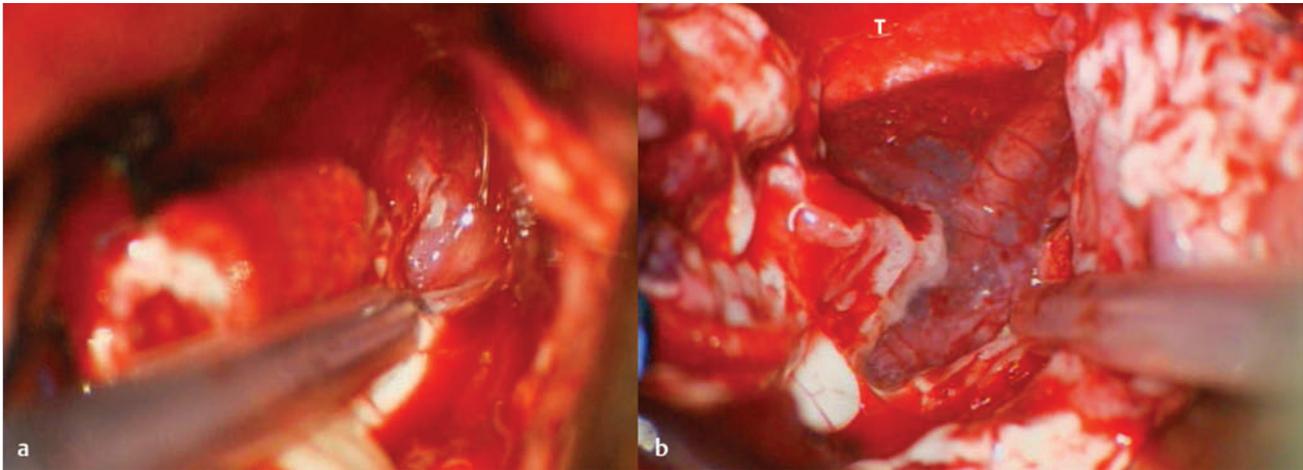


Fig. 72.10 Mesial subpial resection during a left temporal lobectomy. (a) Just medial to the head of the hippocampus is the intact pia, with neurovascular structures evident underneath. (b) After resection of the tissue off the pia with the ultrasonic aspirator, the third nerve, carotid artery, choroidal artery, and branches are all protected. T, tentorial edge.

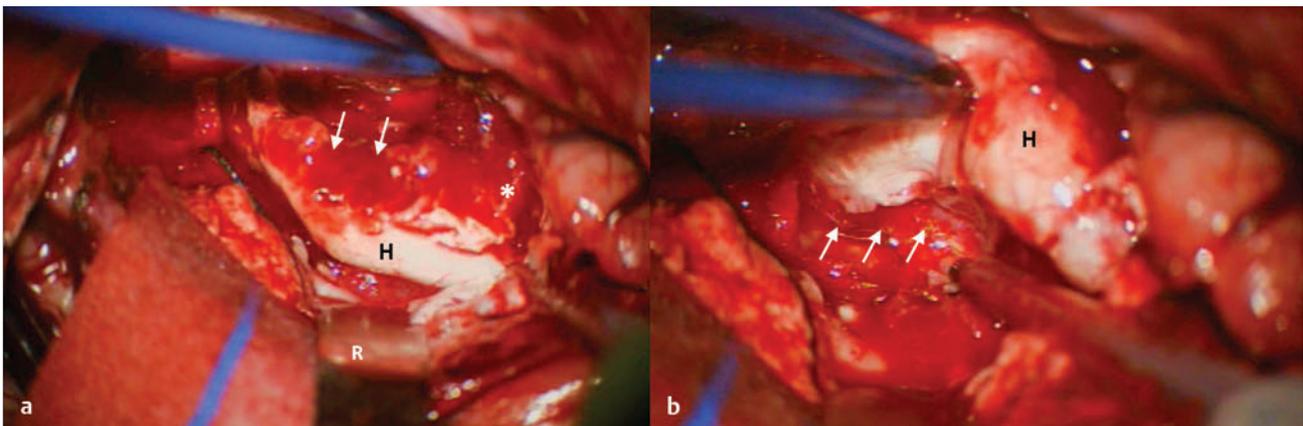


Fig. 72.11 During the medial part of the temporal lobectomy, the hippocampus is skeletonized from inferiorly (a) and along the medial aspect (b). (a) The residual lateral temporal cortex (*) is seen in this right temporal lobectomy. The orientation is surgical—anterior is to the left of the image, inferior to the top. The hippocampus (H) is within the exposed temporal horn. The retractor (R) is placed on the remaining superior temporal gyrus, just superficial to the roof of the ventricle. Arrows indicate the edge of the basal temporal resection at this point. (b) The fimbria of the hippocampus (H) is disconnected from the choroidal fissure (arrows).

the hippocampal head will remain. By looking at the choroidal point, the most anterior portion of the temporal horn, the remainder of the hippocampal head can be seen. Tissue can be taken off the choroidal fissure, starting anterior to the choroid plexus. The tissue is very thin, and only a small amount needs to be aspirated off the fissure. As the resection moves anteriorly and sharply medially, it is taken in front of the midbrain and the medial pia is encountered. The third nerve often will be visible, along with the carotid artery and posterior communicating artery, through the pia (► Fig. 72.10). Coagulation of the mesial pia is rarely necessary, and simple application of a cotton patty is usually sufficient to stop the venous bleeding. This also avoids any coagulation injury to perforators off the carotid or posterior communicating artery that may be just under the mesial pia.

Posteriorly, the choroidal fissure is further exposed. A self-retaining retractor may be used to further expose the temporal horn. Retraction that is too deep or too posterior should be

avoided to prevent injury of the lateral geniculate. Cortical retraction also should avoid injury to adjacent cortex, where, especially on the dominant side, critical regions may be close to the original cortical resection. The fimbria is then resected off the choroidal fissure posteriorly (► Fig. 72.11a). This will be very thin and may have venous bleeding that can be controlled with gentle tamponade, and resection will immediately show the brainstem on the other side of the pia. Posteriorly, the hippocampus will thin, and by 3 cm or so from the head, it will begin to merge with the cingulum and will no longer be along the medial pial surface. The posterior extent can be determined by these anatomical features, along with preoperative MR imaging (e.g., of sclerosis) and presurgical ECoG. The posterior extent is then made with a resection perpendicular to the choroidal fissure that joins the inferior temporal resection with the choroidal resection. Inferolaterally, the hippocampus is freed from the remaining lateral cortex (► Fig. 72.11b). The hippocampus can

now either be resected piecemeal or rolled off the hippocampal sulcus, with ultrasonic aspiration of any adherent areas during the process.

Any remaining hippocampal tissue can be removed with the ultrasonic aspirator, although posteriorly, the medial parahippocampus need not be followed posterior to the quadrigeminal cistern, which sits just behind the typical extent of an aggressive hippocampal removal. Although ECoG may not be useful after lateral resections,⁷¹ the outcome in temporal lobe surgery may be better if any residual hippocampus is devoid of ECoG abnormalities.⁷⁰

Hemostasis is achieved by a combination of lining the cavity with Surgical (Ethicon, Somerville, NJ), temporarily applying Gelfoam (Ethicon), and/or tamponading the area with cotton patties. Final hemostasis is verified with the Valsalva maneuver, and dural closure follows along with bone fixation and layered closure of the scalp.

72.4.2 Nonlesional Cases

When the results of MR imaging are negative, or the findings are subtle and/or incongruent with other parts of the evaluation, the anatomical limits are less obvious. The integration of all of the components of the evaluation is particularly important in these situations. If all the evidence points to temporal lobe dysfunction, then a standard temporal lobectomy may be appropriate. This can be confirmed and tailored with ECoG, especially in the hippocampus, where the resection of all interictal abnormalities may be associated with a better outcome.^{70,78} The aggressive approach to interictal abnormalities must be balanced with other data indicating that it is not necessary (or perhaps possible) to leave the patient with a completely normal ECoG. Especially after resection, residual activity may not be relevant to outcome,⁷¹ especially if distant.¹⁰³

If the evidence suggests temporal lobe involvement, the resection of lateral and medial structures is fairly standardized. The superior and middle temporal gyri can be spared while basal and medial structures are resected; thus, it is reasonable to attempt to discern whether these structures are involved. On the other hand, the anterior 2 cm of the basal temporal lobe is likely to be removed in any approach. Surgery in this situation would, of course, avoid entry into the insula or the far posterior temporal lobe such that a full hemifield deficit would be expected. Rather, such regions would be resected only with definitive evidence of their involvement.

Frequently, “nonlesional” cases do have latent pathology. Nearly half of cases of hippocampal sclerosis in children have negative findings on MR imaging,¹⁴ and dysplasias can be quite subtle on MR imaging. In these cases, though, a highly selective approach would seem more likely to miss the pathology.

72.5 Outcome

72.5.1 Complications

Temporal lobectomy is frequently associated with a superior quadrantanopsia. The association of the temporal horn with the Meyer loop makes this a vulnerable track during any lateral approach to the ventricle, including selective corticectomy approaches.¹⁰⁴ The proximity of the midbrain, third and fourth

cranial nerves, and perforating vessels puts them at risk during temporal lobectomy, although the incidence of permanent injury appears to be low.¹⁰⁵ Memory deficits are typically side-specific, with verbal memory problems seen after left-sided surgery⁶⁶ more often than after right. However, preoperative memory and imaging abnormalities play a very strong predictive role, with both poor memory and lesional MR imaging findings resulting in a higher rate of new problems after surgery.⁶⁷ Whether these effects are mitigated by the younger age of pediatric patients undergoing temporal lobectomy is unproven but suspected based on the few series with careful long-term follow-up of surgical patients.^{106–108}

72.5.2 Seizures

Seizure control after temporal lobectomy is superior to that achieved with medical management in adults. This statement is based on level 1 evidence from a randomized clinical trial of surgery versus medical management⁹ and remains the strongest available statement in epilepsy surgery. It is hard to imagine a similar study being undertaken in children because the randomization process was done after the decision for surgery had been made. The seizure-free outcomes for pediatric temporal lobectomy are quite good based on retrospective studies, and the implications for delaying such a good outcome for a year of study are significant.

Lesionectomy would be expected to have a strong short-term outcome, with many series showing seizure freedom in up to 70% of patients at 3- to 5-year follow-up.^{10,14,21} Mesial sclerosis also has a good outcome, along with observable focal cortical dysplasias. Type I dysplasia and nonspecific pathologies do less well, perhaps because of the more diffuse nature of the disease and the (not independent) challenge of defining surgical margins in the absence of a focal lesion. For all types, outcome studies suggest that complete seizure freedom in long-term follow-up is much more elusive than in short-term follow-up. In 15-year follow-up reports of adult temporal lobectomy, rates are well below 50%. Even the 1-year follow-up in Weibe’s study showed only a 50% rate of complete seizure freedom within the year, and only one-third of patients were free of auras. Thus, retrospective and short-term follow-up reports of outcome should be treated with significant skepticism regarding the longevity of results.

72.6 Other Treatments

Attempts to treat temporal lobe epilepsy directly have also been made with Gamma Knife radiosurgery, even in children.¹⁰⁹ Direct thermal ablation with interstitial laser therapy is another intriguing new application,¹¹⁰ although it has not yet undergone extensive clinical testing.

72.6.1 Outcome

Corresponding brain disorders that may be present must be considered in any discussion of the effect of surgery on cognitive development. Surgery removes tissue, and this risk must be balanced with the other factors mentioned. Studies have shown the benefit of surgery,^{111,112} but also that surgery, especially on the dominant side, may be associated with lingering

deficits.^{66,113} The natural history of uncontrolled seizures is poor with regard to intellectual development.¹¹⁴ Certainly, in catastrophic cases, surgery provides clear benefit when successful in seizure control.¹¹⁵ Many of these deficits remain despite successful surgery, including difficulties with learning¹¹⁶ and language development.¹¹⁷ Nevertheless, the studies of long-term intellectual outcome appear to strongly favor surgical intervention overall.¹¹⁸

Neurocognitive problems like anxiety and depression have a strong association with epilepsy and with the stressors of surgery. These problems may not follow the same course as epilepsy postoperatively. Thus, problems like depression must be addressed after surgery, even in the seizure-free patient.¹¹⁹ Quality of life improves after temporal lobectomy, and the psychosocial benefits may be better with earlier intervention, although many psychosocial problems persist even with surgical control.^{120,121} Complete seizure freedom is consistently associated with improved quality of life,¹²² and some studies have shown an improvement in quality of life even with significant, although incomplete, seizure control.^{120,123}

Although the baseline risk for sudden death with epilepsy (SUDEP) may be lower in children,¹²⁴ with mortality driven primarily by associated neurologic conditions, it is still elevated,⁶ and it is compelling that the risk for SUDEP is less following successful epilepsy surgery.¹²⁵ Epilepsy surgery is associated with an estimable improvement in life expectancy¹²⁶ and is cost-effective compared with ongoing medical treatment.¹²⁷ Drugs may not be able to be discontinued completely in many cases.¹²⁸ Despite the efficacy of surgery, access is variable and relies on both patient and provider factors.^{129,130}

Pearls

- Temporal lobe epilepsy is a common form of focal epilepsy in children.
- Intractability can be defined as the failure of two attempted medications. It is much more likely to occur in the face of a lesion.
- Surgery for temporal lobe epilepsy is supported by level 1 evidence of efficacy in adults and by abundant level 3 evidence of efficacy in children.
- Dual pathology, with both a neocortical and a mesial temporal focus, is more common in children.
- Improvement in quality of life depends on postoperative seizure control.
- The cognitive outcome after temporal lobectomy is less clear and likely multifactorial.

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73 Extratemporal Epilepsy Surgery

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Surgical procedures for extratemporal lobe epilepsy (ETLE) have been built on the success of temporal lobe resections. In 1990, the National Institutes of Health adopted surgical resection as an alternative treatment to medication-resistant epilepsy in children.¹ Temporal lobe resection, described in Chapter 72, has demonstrated significant success in reducing seizures in selected children.² A randomized controlled trial for temporal lobe epilepsy revealed improved seizure freedom for patients with surgical intervention versus medical therapy.³ Although it might appear that outcomes after ETLE surgery could approximate those seen after temporal lobe resections, a wide range of pathologies, diagnostic evaluations, and surgical approaches contributes to substantial variability in the outcomes of ETLE surgery.

Extratemporal pathologies account for a substantial majority of cases of ETLE in children, whereas in adults, temporal lobe epilepsy predominates. However, children treated for ETLE may also have temporal lobe involvement as part of an underlying multilobar pathology. Typically, these extratemporal areas are the frontal, occipital, and/or parietal lobes, and eloquent cortex in these regions may be affected. ETLE also presents an additional degree of difficulty in localization because seizures can quickly propagate to additional locations throughout the cortex.

Extratemporal surgical approaches are employed to address a broad range of pathologies, from tumors to malformations of cortical development, vascular lesions, and other genetically inherited disorders.⁴ Each disease state has its own particular evolution, symptom onset, and management strategies, and multidisciplinary experience at a comprehensive pediatric epilepsy center is required to evaluate and treat affected children most effectively.

73.1 Neural Plasticity

The last several decades have seen significant improvement in the management of children with ETLE, and the field has enjoyed a shifting paradigm from one of watch and wait to one of earlier intervention that capitalizes on neural plasticity in the young child. Neural plasticity refers to the various mechanisms involved in the maturation of the developing cortex in children and the ability of the central nervous system (CNS) to respond to changes in its structure or function.⁵ Discoveries in the neuroscience community have fueled new data on neural plasticity and its impact on CNS development.⁶ Apoptosis, neurogenesis, synapse formation, and pruning all play a role in conferring a dynamic environment in the pediatric brain. Language dominance, for example, has been found to be set no earlier than 5 to 6 years of age.^{7,8} Neural plasticity plays a role in making possible a greater extent of surgical resection in eloquent cortex than would otherwise be permissible in adults.

There is evidence that persistent seizure activity limits the degree of neural plasticity in the developing brain and may impact a child's ability to achieve otherwise-anticipated neurocognitive outcomes.⁹ Although plasticity may allow the transfer of function from interhemispheric or intrahemispheric locations, neurocognitive development may be restricted to

suboptimal levels.⁵ In a consideration of the clinical assessment and treatment options for pediatric patients with extratemporal etiologies, possibly with syndromic manifestations, it is necessary to keep plasticity in mind because it may substantially influence surgical outcomes.¹⁰

73.2 Epidemiology: Incidence and Prevalence

An estimated 65 million people are affected by epilepsy worldwide. The incidence in developed countries is nearly 50 per 100,000, and the prevalence is 700 per 100,000.^{11,12} As recognition of the morbidity associated with epilepsy improves, the disease is increasingly being diagnosed and evaluated by pediatric epilepsy teams. It is estimated that recurrent seizures affect approximately 1% of children,¹ and these persistent seizures, if left untreated, are associated with long-term impairment in cognition, intelligence, and quality-of-life measures. It is estimated that 120,000 children in the United States will be evaluated each year for newly recognized seizures,¹³ and epilepsy will be diagnosed in as many as 45,000 of these cases. In addition, as many as 325,000 children ages 5 to 14 years have active epilepsy, and a majority of adults with epilepsy had a childhood onset.¹³ It is estimated that 100,000 to 200,000 patients in this country may be candidates for surgery because 10 to 20% of children with epilepsy meet the criteria for refractory epilepsy.^{14,15} Predictive factors for refractory epilepsy include early onset and an association with such syndromes as West syndrome, Lennox-Gastaut syndrome, and Ohtahara syndrome. More than 3,000 surgeries are performed each year in the United States for pediatric epilepsy, and with increasing recognition of the disease and the improving diagnostic tools available to surgeons and clinicians, this number is likely an underestimate.¹⁶

73.3 Medical Treatment and Definitions of Refractory

Before surgical management for ETLE is considered, otherwise treatable forms of epilepsy must be excluded.¹⁷ The first priority is to determine if adequate medication has been used to treat the epilepsy. Medication-refractory epilepsy is defined as epilepsy that persists or is unresponsive to two first-line antiepileptic drugs (AEDs).^{18,19} Despite optimal pharmacotherapy, the disease of 30% of the 65 million patients with epilepsy worldwide remains resistant to AEDs.²⁰ The selection of AEDs is individually tailored to each child and takes into account the child's developmental stage, the safety profile of the medication, and the presence of comorbidities. AEDs may affect cognitive and behavior functions, and their levels may be altered by other medications. Medications taken for comorbidities may lower the seizure threshold and impact AED selection.²¹ Children taking more than one AED to control their epilepsy are less likely to respond to additional medications, and once two or three medications have been attempted, benefit from pharmacotherapy is

unlikely.⁵ Other predictors of drug resistance include mixed seizure types, neonatal age at onset, abnormal neurologic examination, early seizure breakthrough after treatment with medication, and underlying structural abnormalities.¹⁸ In addition, some children are unable to tolerate the side effects of medical treatment, and this, too, may confer a pharmacoresistant status.

A ketogenic diet may be used to treat drug-resistant epilepsy in children. The ketogenic diet involves altering the ratio of fat intake to protein and carbohydrate intake. A ratio of 4 g of fat to every 1 g of carbohydrate and protein simulates the metabolic state of fasting and has been shown in a randomized controlled trial to significantly reduce more than 50% of seizures in selected pediatric patients.²² The ketogenic diet is the first line of treatment in epileptic disorders resulting from mutations in the genes for glucose transporter proteins and mutations that cause pyruvate dehydrogenase deficiency. The ketogenic diet is contraindicated in other metabolic disorders, such as those resulting from fatty acid oxidation or carnitine abnormalities.²³ Dietitians and pediatricians can determine when such diet restrictions are warranted.

Because some children who have epilepsy present with various syndromes, there may be additional risks and considerations that prevent surgical intervention. Cardiopulmonary and coagulation status and other comorbidities should not be excessive when surgical options are pursued. Finally, the results of a diagnostic work-up with various studies discussed in the following sections of this chapter should be concordant and implicate an epileptogenic region amenable to resection.

73.4 Common Semiologies by Lobe

The first step in identifying an epileptogenic zone for surgical resection is to use the information on seizure semiology to improve lateralization and localization.^{24,25} An assessment of semiology, or the observable manifestations of seizures, begins by combining historical information provided by the patient and family with video electroencephalographic (EEG) recordings. Descriptive terminology for seizure semiology has been introduced and is supported by the International League Against Epilepsy (ILAE) to improve the significance of localization and the recognition of semiologic features.²⁶ Studies in pediatric patients have helped to identify semiologies that are common to anatomical regions or structures based on EEG findings and that are eradicated following surgical resections. Although misleading in certain cases, semiologies often provide additional clinical information for localizing ictal onset.

Seizure semiologies may be difficult to detect in clonic, tonic-clonic, atonic, gelastic, and myoclonic seizures because they have a generalized onset and nonlocalizable features. These seizures may originate from subcortical regions, such as the thalamus, that generate synchronous activity with extensive ictal spread. A subset of generalized seizures may also have a focal onset that can be identified on EEG recordings, and definitive localization in these seizure types is difficult, so that additional diagnostic studies are warranted. There is also current debate about whether infantile spasms constitute a generalized or a focal seizure type.²⁴ Seizures that involve sustained lateral

deviation of the eye, head, or trunk from the midline are known as versive seizures and can indicate multilobar involvement.

The following semiologies refer to an anatomical location; however, one-to-one correlation is not necessarily the rule because there may be degrees of overlap with adjacent cortical regions. The semiology of seizures may evolve as a child ages, and these changes must be considered. As the myelination of white matter pathways evolves in the first decade of life, intrinsic pathways develop to inhibit seizure propagation, causing the seizure semiology to more closely resemble adult patterns.²⁷ Caution and confirmatory studies should be employed to identify concordant information for seizure localization.

73.4.1 Temporal Lobe Seizures

Seizures that lead to alterations in cognition, attention, memory, or other executive functions are often related to a temporal lobe origin. If the temporal lobe is involved unilaterally or bilaterally in seizure onset, there may be altered consciousness, verbal and nonverbal behavior, and postictal memory loss. In addition, temporal lobe seizures may present with various combinations of olfactory, gustatory, and pharyngeal auras. Auras may also originate from multilobar involvement. Other aura types, such as visual hallucinations, are associated with involvement of the parietal and/or occipital lobes. Finally, oral and upper extremity automatisms may also originate from the temporal lobe, whereas other automatisms, such as bicycling, may be related to frontal lobe pathology.

73.4.2 Frontal Lobe Seizures

Frontal lobe seizures are the most common ETL and account for approximately 20 to 30% of childhood epilepsies.²⁸ Frontal lobe seizures also comprise a significant portion (15 to 30%) of medication-resistant epilepsies. Seizures in the frontal lobe have far-reaching effects and may manifest with a host of possible deficits in children. Children who have frontal lobe epilepsy present with impaired motor and executive function and with socialization, behavior, speech and language, and cognition problems. Behavioral dysfunction manifests as disinhibition, aggression, or attention disorders. Additionally, when children who have frontal lobe epilepsy are compared with patients who have temporal lobe–based or absence seizures, the children with frontal lobe ictal zones have more difficulty with perceptual organization, self-regulation of behavior, impulse control, visual and auditory attention, and visual working memory.²⁹

Frontal lobe seizures present with variable semiologies that include hypermotor activity with repetitive movements in the upper extremities and can be associated with loss of consciousness. Hypermotor activity in children is also a prominent component of seizures originating in the temporal lobe and may decrease with age. In contrast, diminished motor activity, or hypomotor seizures, tends to arise from temporal or parietal locations.²⁴ In children younger than 7 years, frontal lobe epilepsy presents with subtle behavioral changes that differ from those in adolescents or adults. Frontal lobe seizures may also present with a diffuse warm feeling throughout the body or as an altered sensation in the body. Postictal wiping of the nose can occur in patients with frontal lobe seizures; however, this is more common in those with seizures of temporal lobe origin.³⁰

Benign rolandic epilepsy is one of the most common childhood epilepsies, with an estimated incidence of 5 to 15% of pediatric epilepsies.³¹ It is characterized by transient simple partial seizures with hemiparesis, facial palsies, difficulty swallowing, hypersalivation, and oromotor apraxia.³² These seizures have a typical presentation pattern in children 3 to 10 years of age and may spontaneously remit by adolescence. The seizures frequently occur during sleep or shortly after awakening, and neurocognitive studies are often normal in these children.³¹ Multidisciplinary epilepsy teams, however, are becoming increasingly aware of a certain population of children in whom rolandic seizures were previously diagnosed who present at earlier ages (younger than 6 years) and have progressive cognitive impairments. These children are diagnosed with malignant rolandic epilepsy³³ that is refractory to antiepileptic medications and whose semiology may change. The term *malignant* is used to identify the increased frequency and clustering of seizures, resistance to medical therapy, and longer duration of the disorder. The seizures may also involve somatosensory symptoms and can generalize to tonic-clonic seizures.^{32,34}

73.4.3 Parietal Lobe Seizures

Parietal lobe seizures account for only 5% of partial seizures despite their large cortical volume.³⁵ The semiology of the parietal lobe is difficult to detect because epileptic activity may rapidly spread from ictal foci to adjacent lobes, triggering events that are seen as originating from the temporal or occipital region.³⁶ The parietal lobe subserves several eloquent cortical functions, including integration of visual information, language, praxis, and attention. Parietal lobe damage results in apraxia, agnosia, agraphia, acalculia, left-right disorientation, hemineglect, and altered body image.³⁷

Parietal lobe seizures involve visual or somatosensory auras that can be localized to a particular region of the patient's body.³⁸ In addition, parietal lobe seizures present with ictal pain, complex visual hallucinations, and autoscopia (out-of-body experience).³⁶ Seizures originating from the parietal region can quickly spread to the temporal lobe and present with semiologies similar to those of temporal lobe epilepsy.

73.4.4 Occipital Lobe Seizures

Occipital lobe epilepsies account for an estimated 8 to 28% of partial epilepsies in children,³⁸⁻⁴⁰ and some of the earliest reports of seizure semiology in occipital lobe epilepsy were described in 1885.⁴¹ A large number of patients will have Panayiotopoulos syndrome, the second most common childhood epilepsy after benign childhood epilepsy, and do not require surgical intervention because there is a significant rate of spontaneous seizure remission in these patients.⁴² It is estimated that only 2% of epilepsy procedures are done in children with occipital lobe seizures.³⁹ The ILAE has divided occipital lobe epilepsies into two types depending upon early or late onset. Early-onset seizures occur at a median age of 5 years and present with non-visual symptoms, such as vomiting, eye deviation, and tonic head movements. Late-onset seizures occur at a mean age of 9 years and most commonly involve visual hallucinations, followed by illusions, palinopsia (persistence of an image or its recurrence), and visual auras, as well as ictal blindness and

amaurosis with loss of portions of the visual fields.^{40,43} If the seizures spread, temporal lobe automatisms or focal motor seizures may develop if the supplementary motor cortex is affected.³⁹ Children with occipital lobe seizures are also found to have lower verbal and performance IQs and can be at increased risk for neurobehavioral disorders.⁴²

73.5 Diagnostic Work-up

The diagnostic work-up required for children with ETLE has become more advanced throughout its evolution and now includes a host of technologies routinely used by epilepsy centers to identify the etiology of seizures and ictal onset.⁴⁴ The utilization of each test depends largely upon the suspected etiology, and tests may proceed to more advanced technology if the information is discordant. Adding a further layer of complexity to the analysis of children with ETLE is the changing nature of seizure types, as in infants who present with generalized or partial seizures that can evolve to complex partial seizures, absence, generalized tonic-clonic, or myoclonic seizures.

73.5.1 Noninvasive Electroencephalography and Video Electroencephalography

EEG serves as the foundation of inquiry into epilepsy in children. Video EEG units have the added power of coupling longitudinal electrophysiologic data with clinical manifestations to determine the effect of a seizure on a child's function.

Interictal epileptiform discharges (IEDs) often originate from an area of the cortex that is somehow associated or responsible for ictal discharges. In temporal lobe epilepsy, these discharges can be associated with mesial temporal sclerosis or temporal tumors. In ETLE, the use of EEG to identify focal IEDs, such as those seen with focal cortical dysplasia (FCD), is associated with improved surgical outcomes for seizure-free activity. Ictal EEG recordings are helpful for localization in cases with a high degree of recording concordance. Extra attention must be paid in cases of ETLE in which parietal and occipital lobe seizures can cause a false localization. ETLE in the frontal lobe can frequently present with focal rhythmic fast activity on EEG. Scalp EEG source localization is an additional technique used to identify the epileptic center of activity and may be of use in preoperative studies of ETLE.⁴⁵

Although EEG remains the cornerstone for the evaluation of ETLE, it has limitations when pediatric patients present with the synchronous onset of epileptiform activity over a diffuse epileptogenic area, which represents multilobar pathology. Additionally, there can be poor localization with EEG, an absence of IEDs, or no appreciable EEG changes with clinical seizure onset. These limitations reduce the likelihood of identifying the ictal onset in ETLE and warrant the performance of additional diagnostic studies. High-frequency oscillations (100 to 500 Hz) are associated with epileptic regions in the hippocampus and neocortex⁴⁶ and may be used as biomarkers for epileptogenic regions.⁴⁷ Prospective studies to correlate high-frequency oscillation rates with zones of seizure onset are ongoing and will determine the predictive value of this technology.^{48,49}

73.5.2 Neuroimaging

Neuroimaging modalities and their uses in diagnosing the etiologies of pediatric ETLE have seen significant changes over the past 20 years and may be the most important sources of improved presurgical planning in children with ETLE. With improved resolution, magnetic resonance (MR) imaging has helped to detect previously unidentified brain lesions. Field strengths in excess of 1.5 tesla (T) and phased-array coils are increasingly being used for volumetric studies and localization in a clinical setting.⁵⁰ The use of 3-T imaging increased the identification of lesions in 65% of patients previously reported to have negative images.^{51,52} Although lesions are more clearly viewed, their contribution to the onset or persistence of epileptiform activity must be correlated with clinical and electrophysiologic data, such as EEG recordings.

Seizure-free outcomes are improved when EEG and neuroimaging modalities are concordant.^{53,54} If, however, the patient has multiple lesions or other associated malformations of cortical development (MCDs), additional evaluation with diagnostic studies is warranted. Despite the increasing reliance on MR imaging to localize lesions, seizure freedom has been successfully achieved⁵⁵ in patients in whom no appreciable lesion could be identified on MR imaging.^{56,57} The use of intracranial EEG (iEEG),⁹ positron emission tomography (PET), and ictal single photon emission computed tomography (SPECT) improved surgical outcomes in 75% of patients, with a 37% seizure-free rate in cases in which MR imaging was unsuccessful in localizing a lesion. Surgery remains a treatment option even when the results of MR imaging are equivocal.

Questions arise about which pediatric patients should be screened with MR imaging. When a child presents with a first-time seizure, computed tomography (CT) is usually performed in the emergency department, with one-third of these patients later determined to have epilepsy. Previous studies have shown that 7 to 24% of CT procedures identify abnormalities warranting management.⁵⁸ MR imaging is the next imaging modality for evaluating children; however, 50% of imaging studies in patients with idiopathic generalized epilepsy are normal. The threshold to obtain MR imaging in infants is lower because they are at an increased risk for developmentally related malformations that may manifest without otherwise localizable features.⁵⁴ Children who should also undergo early MR imaging are those with focal seizures, abnormal or focal neurologic examinations, developmental delay or regression, generalized epilepsy, signs of increased intracranial pressure, or syndromic manifestations or family histories of epilepsy.⁵⁸ Pediatric neuro-radiologists familiar with developmental changes in the appearance of the cortex are required for the optimal screening of MR imaging findings.⁵²

Many protocols have been developed by various centers to optimally image pediatric epilepsy-related pathologies. Most surgical centers require thin-slice volumetric T1-weighted images with and without contrast, T2-weighted images, and FLAIR (fluid-attenuated inversion recovery) images in an axial, coronal, and sometimes sagittal reconstruction. Volumetric MR images have also been useful to identify hippocampal volumes to determine if a component of mesial temporal lobe sclerosis is present. MR imaging is paired with MR spectroscopy to identify markers of neuronal loss and the presence of certain tumors or

other abnormalities. MR imaging has helped not only to identify congenital MCDs, tumors, and other abnormalities, but also to confirm in an intraoperative setting the complete resection of lesions, thereby reducing the need for additional surgery.⁵⁹ Still, the lesions of 20 to 30% of patients are not localized with MR imaging.⁶⁰

As the number of cryptogenic cases of ETLE increases at pediatric epilepsy centers, newer MR technologies are pushing the boundaries to identify underlying lesions. These techniques are being applied primarily to FCDs that result from abnormal cortical development and migration defects. Structural MR imaging is employed to look for subtle abnormalities in gyral and sulcal morphometry. Voxel-based intensity and morphometric studies are used along with quantitative image analysis⁶¹ to identify lesions through automated pattern recognition.⁵⁷

Diffusion tensor imaging (DTI) and tractography rely on the anisotropic diffusion of free water to identify white matter tract organization. The use of DTI for preoperative planning⁶² is rapidly expanding, and DTI has aided in the identification of optic tract,⁶³ motor strip, and other eloquent cortical involvement in and around epileptogenic foci. DTI can also reveal changes that occur in patients with certain pathologies⁶⁴ or with language and memory impairments, and the results can be correlated with neurocognitive outcomes.⁶⁵ DTI is used to obtain high-resolution functional and structural data that can guide the stereotactic placement of subdural EEG electrodes in ETLE cases.⁶⁶ DTI improved surgical decision making in 66% of patients, and its use is correlated with improved surgical outcomes for ETLE.⁶⁷ Following surgery,⁶⁸ DTI may also be employed to assess the plasticity of the underlying cortex and remodeling in fiber bundles.⁶⁹

73.5.3 Functional Magnetic Resonance Imaging

Functional MR imaging (fMRI) is an additional use of MR imaging that maps cerebral activity by detecting changes in blood flow while a patient performs associated tasks. fMRI works by detecting the level of deoxygenated hemoglobin, which decreases when a cortical area is activated, thereby increasing blood flow to that cortex.⁷⁰ This technique, called blood oxygenation level-dependent (BOLD) contrast fMRI, has been useful in mapping language function.⁷¹ fMRI can be successfully performed in children as young as 5 years of age in whom the lateralization of motor and other functional capacities has already been established.^{27,58} fMRI techniques are used to lateralize language function in the temporal lobe to aid in preoperative evaluation.⁷² fMRI can also be used in preoperative studies to assess motor tasks.^{73,74}

73.5.4 Functional Connectivity Magnetic Resonance Imaging

Recent advances in fMRI use spontaneous BOLD fluctuations to map functional connectivity in the brain. A normal brain that is not performing a task exhibits slow (<0.1 Hz) fluctuations in the BOLD signals that correlate with neuronal activity⁷⁵ in a distinct functional network. Functional connectivity MR imaging (fcMRI) can be performed in children at rest to identify

sensorimotor and language cortical regions. There are several advantages to using fMRI in children because they are not required to perform an age-dependent or cognitive-dependent verbal or motor task. Thus, children may be investigated at earlier ages. In addition, a single study will allow the deciphering of various functional connectivity networks with improved signal-to-noise ratios.⁷⁶ The future use of fMRI in preoperative evaluations may improve our understanding of anatomical connectivity and function in pediatric ETLE.⁷⁷

73.5.5 Positron Emission Tomography

PET is increasingly being used to determine areas of ictal onset by identifying hypometabolic regions corresponding to abnormal cortex.⁷⁸ PET uses fluorodeoxyglucose (FDG) to approximate metabolic activity in the cortex. Hypometabolic FDG-PET has been used to identify and localize regions of suspected epileptogenesis that require additional investigation. In addition, α -methyl tryptophan (AMT)-PET is used to differentiate between epileptogenic and nonepileptogenic lesions in patients with tuberous sclerosis and MCDs. Finally, flumazenil (FMZ)-PET⁷⁹ can identify epileptic cortex beyond an abnormality on MR imaging by detecting areas with decreased binding to γ -aminobutyric acid A receptors.¹ PET has the advantage of using different receptor binding sites in the brain, which facilitates ongoing investigations into the neurobiology of epileptogenesis.⁷⁸

73.5.6 Single Photon Emission Computed Tomography

SPECT approximates perfusion to a suspected area of cortical involvement in epileptiform activity following the injection of a radioactive tracer. Focal increases in perfusion reflect epileptic activity. Ictal SPECT measurements approximate metabolic demands and may localize hypermetabolic lesions like FCD when conventional MR imaging is equivocal. Studies can be compared in which subtracted ictal–interictal SPECT data can increase the sensitivity for detecting differences between perfusion rates in the ictal and interictal states. The resulting information can be co-registered with MR imaging (subtraction of interictal from ictal SPECT co-registered to three-dimensional MR imaging, or SISCOM) to identify epileptic foci.⁸⁰ In cases of tuberous sclerosis⁸¹ and other multifocal abnormalities, SPECT is especially useful for defining the epileptogenic zone. Co-registration with MR imaging can also be employed to guide and implant subdural electrodes. Ictal SPECT has limitations, however, because it is difficult to synchronize the timing of the injection radioactive tracer with ictal onset, and close video EEG and clinical monitoring by a trained multidisciplinary epilepsy team are required.

73.5.7 Magnetoencephalography and Magnetic Source Imaging

MEG is a more recent technology that is increasingly used to identify magnetic fields and dipole clusters produced by cortex with interictal epileptiform activity. In turn, MEG can detect electrical activity that is parallel to the cortex and tangential to the convexity.⁸² The magnetic fields are not dissipated by the

intervening structures of the skull and scalp, which aids in localization. MEG results have been verified by correlation with iEEG recordings and have improved localization in equivocal cases in which video EEG and MR imaging appeared to be discordant. The accuracy of MEG for predicting surgical outcome was compared with that of MR imaging and various EEG techniques and was found to be second only to that of intracranial subdural EEG monitoring.^{83,84} In a study of ETLE, concordance between MEG and iEEG data in localizing epileptiform discharges corresponding to the ictal zone was found in 91% of children.⁸⁵ The future applications of MEG may reduce the number of patients requiring invasive studies, leading to a more cost-effective and safe use of diagnostic studies in children.⁸⁶

Failure to remove regions with active preoperative MEG dipoles predicts postoperative seizure recurrence.^{87,88} MEG is being increasingly used to reduce the number of studies required to evaluate infants undergoing hemispherectomy.⁸⁹ Some epilepsy centers are turning to MEG as a primary modality to identify the ictal area during preoperative planning and resection.⁹⁰ MEG has the ability to map sensorimotor, language, and other functional capacities, and its accuracy is comparable to the perceived gold standard of iEEG monitoring.⁹⁰

In magnetic source imaging (MSI), MEG and MR imaging data are combined to optimize the results of each modality for structural and functional data. Three-dimensional images can be generated to delineate the morphological and functional changes wrought by epileptogenic tissue.⁹¹ Epileptic foci can be accurately pinpointed with this technique and compared with eloquent cortical regions or detectable structural abnormalities.⁹² This information can guide surgical resections or lead to palliative procedures, such as multiple subpial transections. MSI correlates with surgical findings in more than 89% of cases⁹³ and has a reported accuracy of 100% in ETLE cases.⁹¹ MSI improved localization data in 35% of patients and altered treatment decisions in 10% of patients. In cases of tuberous sclerosis, MSI has a reported 100% sensitivity, 94% specificity, and 95% accuracy in identifying epileptogenic lesions in children.⁹⁴ MSI data can also be used to predict surgical outcomes.^{31,95}

73.5.8 Wada Test

The intracarotid injection of sodium amobarbital (Wada test) is used to study the function of a cerebral hemisphere. Following injection, the ipsilateral hemisphere is temporarily inactivated, and language and memory function in the contralateral hemisphere can be tested to localize these functions. Wada testing is limited because it is invasive, and it may be supplanted by fMRI or MEG in the future.

73.5.9 Neurocognitive Testing

There is growing recognition that seizure freedom is not the only measure of a successful outcome postoperatively. A number of neurocognitive tests have been developed to monitor preoperative deficits and postoperative outcomes, with the goal of improving the pediatric patient's quality of life following intervention. Each patient undergoing surgical evaluation requires a complete neurocognitive evaluation to identify cognitive function, language skills, intelligence, attention, memory,

executive function, personality, behavior, and motor and sensory limitations. Children with epilepsy have a higher rate of comorbidities when compared with control groups. Childhood comorbidities in epilepsy include attention-deficit/hyperactivity disorder (ADHD), autism, depression, anxiety, developmental delay, and cognitive and behavioral abnormalities. Symptoms of ADHD were identified in 38% of children with epilepsy, and depression and anxiety were seen in 26% and 16% of epileptic children, respectively.⁹⁶ Epilepsy is found in 28% of autistic children.¹³ Finally, the incidence of mental retardation and cerebral palsy is upward of 38% in children with epilepsy.⁹⁷

Despite extensive evaluation and a combination of various noninvasive modalities to localize the epileptogenic region, a considerable fraction of children with medically refractory ETLE will require iEEG monitoring with invasive techniques. These patients often have normal or nonlocalizing imaging, widespread EEG abnormalities, or multiple lesions. To pursue subdural monitoring with grids, strip, and depth electrodes, input from an experienced epilepsy team is warranted.

73.6 Surgical Decision Making: Epilepsy Center Structure

Seizure freedom is the ultimate goal in a neurosurgical intervention for pediatric epilepsy. In some cases this may be an unachievable goal, however, and palliative procedures are offered to reduce the seizure burden. Managing the expectations of families adds a further layer of complexity to the treatment of ETLE.⁹⁸ As the scientific and clinical communities have increasingly recognized the difficulties associated with ETLE treatment, there is a preferred exclusion of patients based on extratemporal locations.⁹⁹ To obviate such an approach, patient selection and knowledge of the various syndromes and seizure types become essential components of surgical planning and decision making.¹⁰⁰ Parental angst may be offset by the collective experience offered by pediatric epilepsy centers for difficult cases.

Multidisciplinary meetings with epileptologists, neurosurgeons, radiologists, EEG technicians, neuropsychologists, pediatricians, therapists, and other associated healthcare providers facilitate the summation of the information collected for each child who is a potential surgical candidate. During these meetings, the diagnostic information obtained with video EEG, semiology, and neuroimaging, together with potential surgical planning, is used to frame possible solutions to reduce or eliminate seizure burden. As a result of collective experience and discussions, aided by improved diagnostic techniques, increasing numbers of children are being considered for surgical intervention. Cost analysis in developing countries reveals that lesions can be cost-effectively treated with limited resources. Ideal patients are those with lesions identified by MR imaging that have been co-localized with interictal and ictal EEG.⁹⁹

With a multidisciplinary approach and the success of surgery in ETLE, there is a growing trend to identify children as early as possible for surgical intervention and to select patients who are at high risk for failing medical therapies. The early identification of surgical candidates is one goal of surgical centers, where children can be evaluated expeditiously instead of waiting for prolonged unsuccessful medical treatments. There is a balance that must be struck in the early identification of children with

surgically amenable pathologies. Adequate medical therapy should be advocated while the selection of surgical candidates is improved. Children with infantile spasms, multiple seizure types, or recurrent seizures within 1 year of treatment are likely to progress to intractable epilepsy that may also require surgical intervention and are less likely to respond to medical therapies.²⁷ Patients who have syndromes associated with ETLE may also benefit, with surgery considered for those with Sturge-Weber syndrome, tuberous sclerosis, FCD, hemimegalencephaly, Rasmussen syndrome, or low-grade tumors. With a greater understanding of seizure types and the neurodevelopmental burden of seizures, it is clear that more children can now be helped.^{8,101}

There are also patient variables that make seizure-free outcomes less likely in surgical candidates. Diffuse lesions on MR imaging, seizures with a neonatal onset, a longer duration of epilepsy, psychiatric comorbidities, and IQs below 70 have all been associated with poorer postoperative outcomes. Patients undergoing multilobar resections are also less likely to achieve seizure-free status. In addition, the histopathologic diagnosis of a tumor is associated with an improved surgical outcome in comparison with FCD.¹⁰² The seizure-free outcomes of FCD type II may be better than those of type I as a result of improved visualization with MR imaging to aid complete surgical resection.

Epilepsy teams are also charged with evaluating the pediatric patients in follow-up, looking not only for degree of seizure remission or freedom but also for neurocognitive outcomes and, ultimately, the ability to function independently in society.

73.7 Surgery

The surgical resection of epileptic foci in pediatric patients began with Victor Horsley in 1886.⁸ Initial results from these efforts suggested a reduction in seizure frequency and tolerable clinical outcomes. With the later availability of EEG, Wilder Penfield pursued epilepsy surgery at the Neurological Institute in New York and later founded the Montreal Neurological Institute while pioneering the use of electrocorticography (ECoG) to guide surgical resections of epileptogenic tissue.¹⁰³ During his studies, Penfield focused primarily on adult pathology and temporal lobe epilepsy, but he also performed a significant number of surgeries for ETLE.^{104–109} This and other groundbreaking work slowly led to the expansion of surgical techniques in children.^{110,111} Continued progress in clinical studies in the 1980s and 1990s led to the increasing appreciation that younger patients with ETLE were surgical candidates. While hemispherectomy and other disconnection surgeries were gradually adopted into the realm of pediatric epilepsy, a host of new surgical techniques, paired with advancements in diagnostic techniques, paved the way for extratemporal surgery in a pediatric population.

73.7.1 Single-Stage Procedures

The most straightforward application of surgery for the treatment of ETLE in children is single-stage surgery for lesionectomy or lobectomy. When the aforementioned diagnostic tools (MR imaging, EEG and clinical data) are concordant in their localization of a lesion responsible for seizures,

surgical resection is pursued. Children with a resectable offending lesion have the best seizure-free outcomes, with results related to a gross total resection. Advanced diagnostic tools like PET and SPECT may be avoided in children in whom concordant results identify a single lesion.

During surgery, ECoG is often used to identify interictal data and functional cortical regions. ECoG remains the gold standard for the evaluation of an ictal onset and can be performed during surgical resection, after the implantation of subdural grids, or following surgical resection to evaluate areas for ongoing epileptiform activity. General anesthesia without benzodiazepines is preferable.¹¹² A larger craniotomy will allow mapping of the cortical surface. Depth electrodes may be placed with frame-based or frameless stereotactic systems that can also be used to guide surgical resection. ECoG requires that grounding and reference electrodes be placed subgaleally or on the scalp surface.

Cortical mapping is possible during surgery with somatosensory evoked potentials (SSEPs) and bipolar cortical stimulation.¹¹³ Low stimulus settings can be used to avoid eliciting seizures and may be tailored according to the age of the patient. Settings for cortical stimulation may include 3- to 5-mA, 50-Hz biphasic square wave pulses with a duration of 0.3 millisecond.¹¹⁴ The current can be increased in small intervals until an ictal event or afterdischarge is seen or if a current of 15 to 16 mA is reached. Likewise, the pulse duration may be increased in a stepwise manner until a duration of 1 millisecond is achieved. The central sulcus may be identified by phase reversal in SSEPs, and motor evoked potentials may be used to further identify regions of the motor cortex. The response to motor cortex stimulation is related to the age of the patient, with infants showing no response given the underdeveloped myelination of the major motor pathways. Seizures that are elicited on ECoG can be aborted with the application of cold saline to the cortical surface.^{115,116}

After ECoG and cortical mapping, resection of the lesion is pursued while the boundaries of eloquent cortex are respected. Multiple subpial transections, discussed later in this chapter, may be used if the ictal region involves eloquent cortex. Efforts should be made to avoid the retraction of normal brain to avoid vascular compromise, infarct, and postoperative edema. If a lesion is present, ultrasound or frameless MR imaging neuronavigation may aid in identifying the limits of surgical resection, and a lesionectomy can be performed. If only epileptogenic cortex is present, a corticectomy is performed, in which the gray matter is removed with a subpial dissection technique down to the white matter. Care is taken to follow the gyral folds to the depths of the sulcus to avoid leaving epileptic tissue behind. ECoG after resection allows confirmation of complete resection of the ictal focus. Postoperatively, anticonvulsants are continued according to the patient's previous home regimen and may be tapered based on close observation by pediatric neurologists.

73.7.2 Two-Stage Procedures

The current technology of diagnostic imaging and electrophysiology can be stretched to its limits as the complexity of cases addressed by pediatric epilepsy teams (younger ages of patients, increased comorbidities, syndromic findings) increases. Frequently, discordant data cloud localization of the area of ictal onset. One technique that improves a neurosurgeon's ability to

diagnose and treat ETLE is the use of subdural electrodes for neurophysiologic recordings and ECoG.¹¹⁷

The implantation of electrodes for iEEG monitoring has gained popularity in the last decade, largely to address the number of patients who have discordant diagnostic studies or who have lesions adjacent to eloquent cortex.^{32,118} The benefit of iEEG is that children who were previously not surgical candidates can now undergo invasive studies so that a surgical approach can be tailored to their particular underlying pathology. iEEG with electrodes allows longitudinal monitoring, which can better identify epileptogenic cortex and further map eloquent areas. Ictal and interictal activity can be studied, and cortical stimulation can be employed to identify motor, speech, and language areas in children who are of an age to have these localizable functions identified. In addition, stereotactically placed depth electrodes are used to probe subcortical regions where activity is not otherwise recorded by superficial grid arrays.^{119, 120} Neuronavigation with frame or frameless stereotactic systems is also routinely employed to take advantage of MR imaging that has been fused with MEG, PET, and/or SPECT data. The combination of neuronavigation with these diagnostic modalities improves surgical planning and identifies nearby eloquent cortex that limits resection.

The first stage of surgery involves using the aforementioned diagnostic studies to identify areas of interest either in one or both hemispheres that are candidates for iEEG monitoring. Preoperatively, epileptologists and neurosurgeons can design an optimal array of strip, grid, and depth electrodes to obtain the necessary electrophysiologic information and to maximize coverage of the cortical surface (► Fig. 73.1a). Detailed thin-cut MR imaging with venography or arteriography can aid in surgical planning, especially if stereotactic localization is used. Subdural grids are especially useful for assessing the interhemispheric cortex, orbital frontal cortex, mesial temporal lobe, and cingulate gyrus. The implanted arrays are silicon-covered platinum-indium electrodes that are MR compatible and allow postoperative imaging to confirm anatomical localization (► Fig. 73.1b,c). After placement of the subdural electrodes, epilepsy teams will note the location and orientation of the arrays, often with intraoperative photographs for later matching to imaging and iEEG data (► Fig. 73.1d). To augment the information offered by surface array coverage, depth electrodes can safely be employed in cases of ETLE to target cortex that may lie tangentially to conventional strip or grid electrodes (► Fig. 73.2a). The electrophysiology of sulci and regions like the interhemispheric cortex and frontal and temporal opercular cortex may also be probed (► Fig. 73.2b) with depth electrodes.¹²¹

Electrode wires are tunneled out through the skin with separate stab incisions (► Fig. 73.2c) and anchored to the dura and skin with purse-string sutures. This reduces the opportunity for electrode migration during closure of the surgical incision and postoperative studies. A duraplasty may be necessary to accommodate the bulk of the arrays. Replacement of the cranial bone flap (► Fig. 73.3a,b) depends upon surgical technique because there are options to hinge the bone flap without complete removal during surgical exposure. Other options are to replace a fully removed bone flap after lead placement or to store it in a freezer for later replacement. Each technique has its advantages and disadvantages. A hinged bone flap obviates the need for additional titanium hardware placement and preserves

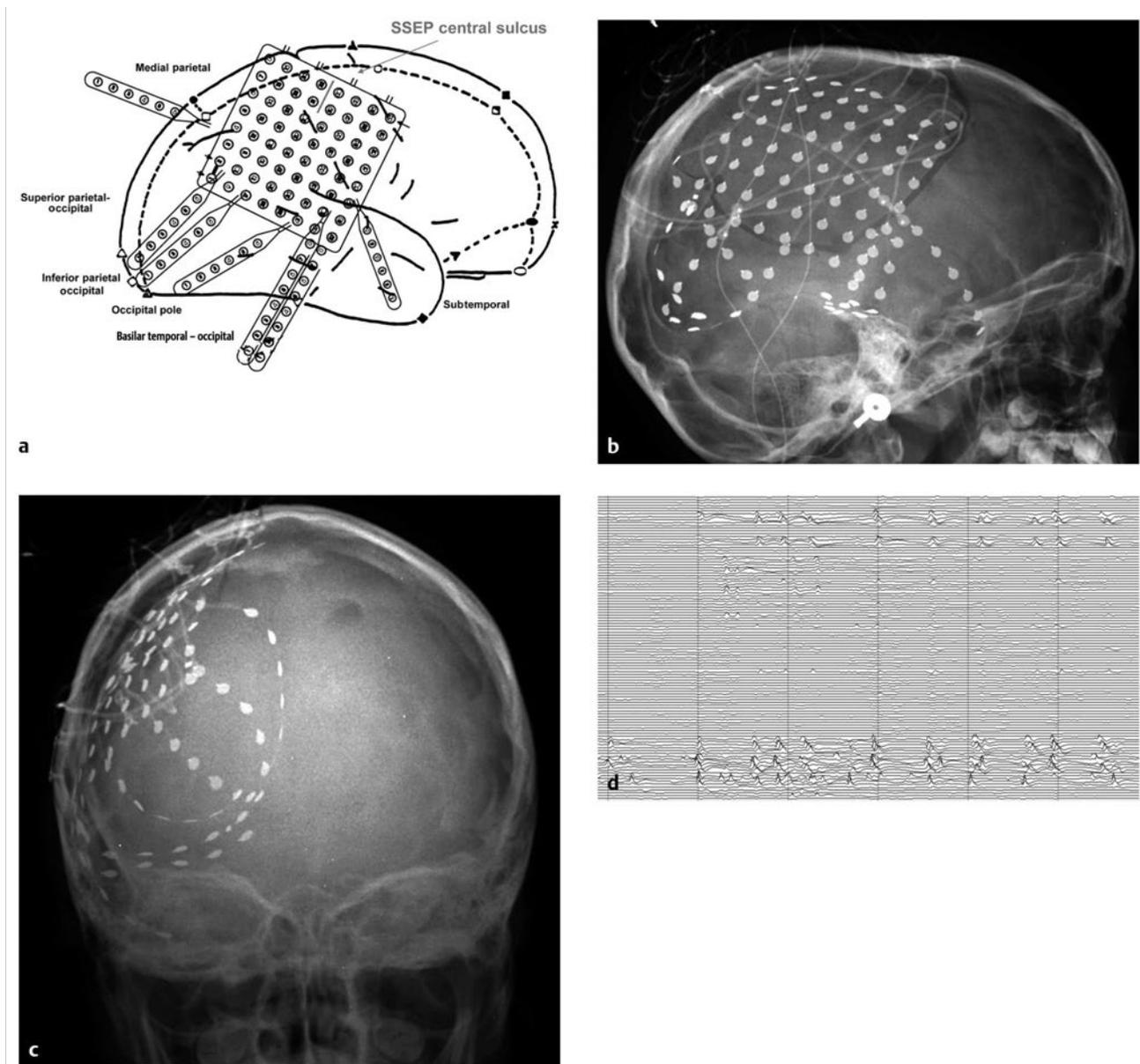


Fig. 73.1 Ictal localization for a parieto-occipital resection. (a) Pictorial representation for planning the placement of the grid array with respect to the cortical surface. The 8 × 8 grid can be seen, with adjacent six-lead strip electrodes overlying various portions of the cortex. The central sulcus is marked under the overlying grid. SSEP, somatosensory evoked potential. (b) Postoperative lateral plain radiograph revealing placement of the array of grid and strip electrodes for ictal localization. The underlying craniotomy can be seen with lucency in the calvaria. (c) Postoperative anteroposterior plain radiograph revealing the same placement of the grid array and strip electrodes. (d) Electroencephalogram from placement of the grid and electrodes localizing epileptic activity with spike-wave complexes to the occipital lobe.

anatomical perfusion and aesthetics. There may, however, be limitations in the degree of exposure. Replacement of a bone flap following lead placement protects the underlying cortex and monitoring devices, but it may constrict the additional volume of subdural grids, subdural fluid, and edema, potentially causing a mass effect. Finally, storing the cranial flap in a freezer may alter the native osteogenic repair following replacement in the second stage, resulting in bone flap resorption.

Temporalis fascia and skin are approximated, and postoperative radiographs in the anterior–posterior and lateral positions reveal the anatomical orientation of the grid (► Fig. 73.3b).

Sterile dressings are applied, and prophylactic antibiotics are continued through the second-stage resection and electrode removal. Video EEG can then be performed while the child’s medication is tapered as necessary to elicit habitual seizures. Correlation of the electrophysiologic data with clinical seizure onset is followed by cortical mapping to identify eloquent cortex. The purpose of obtaining iEEG data is to use analysis of the IEDs to localize the ictal onset and epileptogenic tissue that requires excision.¹²² Adequate ictal data are required to proceed to a surgical resection. The presence of focal high-frequency oscillations (>20 Hz) identifies more than 85% of patients with

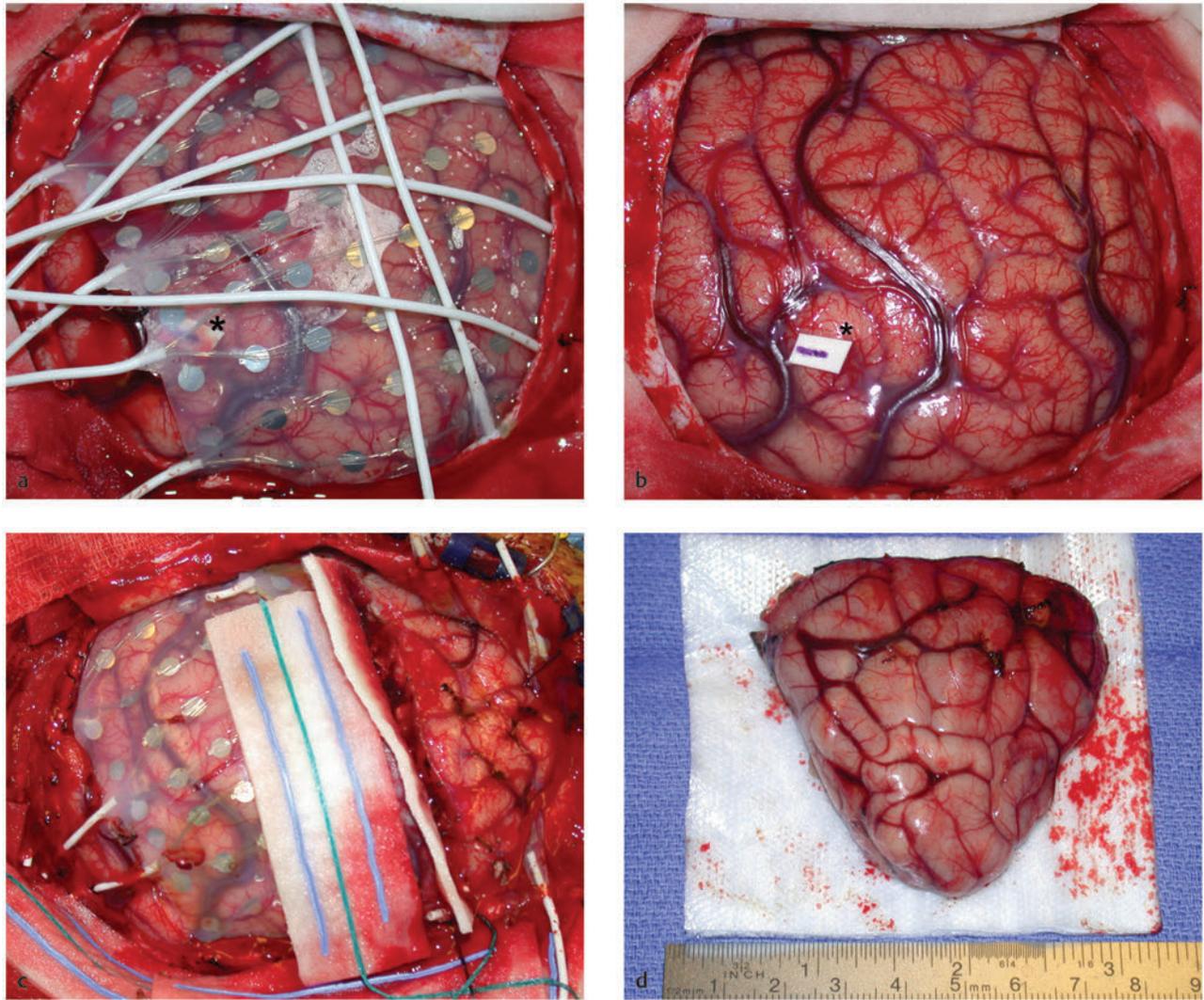


Fig. 73.2 Intraoperative photographs from an occipital lobe resection. (a) This photograph reveals the grid array over the affected cortical surface. Asterisk (*) represents underlying hand motor cortex. (b) Image of the cortex with the grid array removed and revealing the underlying mapped hand motor cortex. Asterisk (*) represents the hand motor cortex adjacent to the placed marker. (c) Intraoperative photograph revealing the initial resection bed. The grid is left in place to guide resection of the ictal focus. The beginning of a corticectomy is seen. (d) Photograph of the en bloc resected epileptogenic tissue.

ETLE who are likely to achieve a seizure-free outcome⁶⁰ and may play a role in localization of the seizure onset. Studies are ongoing. Additional spectral analysis for the presence of high-frequency oscillations on iEEG data in pediatric cases of ETLE may yield additional insight as to who may benefit from surgical resection.⁴⁵

Before the second stage, MR imaging is often performed to identify the cortical orientation of the arrays, and it allows the gyral anatomy to be understood in relation to the iEEG data. Radiographs before surgery are used to verify if the leads have migrated from their position on immediate postoperative studies. Changes in surgical planning may be warranted if shifting of the electrodes is suspected. The second craniotomy is performed, and the area for planned resection is marked before the arrays are moved (► Fig. 73.3c,d). A resection of the cortex is completed, and intraoperative ECoG is used to ensure that the in-

volved epileptogenic areas have been successfully removed. Intraoperative ECoG may show decreased spike frequency as a result of general anesthesia.³⁴ During surgery, epileptogenic tissue may be identified involving eloquent cortical functions, or there may be large cortical draining veins whose sacrifice could lead to edema and additional seizures¹¹⁸ (► Fig. 73.3e,f). Multiple subpial transections, a technique described later, are employed in areas of residual epileptic discharges in eloquent cortex.

There are disadvantages to the placement of subdural grids in pediatric patients. These include additional surgical exposure; the risk for perioperative complications of anesthesia, blood loss, and infection; subdural fluid collections; cerebrospinal fluid leak; strip electrode malfunction necessitating surgical replacement; pneumocephalus; and mass effect.¹²³ Monitoring in pediatric patients may also be less well tolerated for prolonged periods of time.⁸ Although concerns exist regarding prolonged

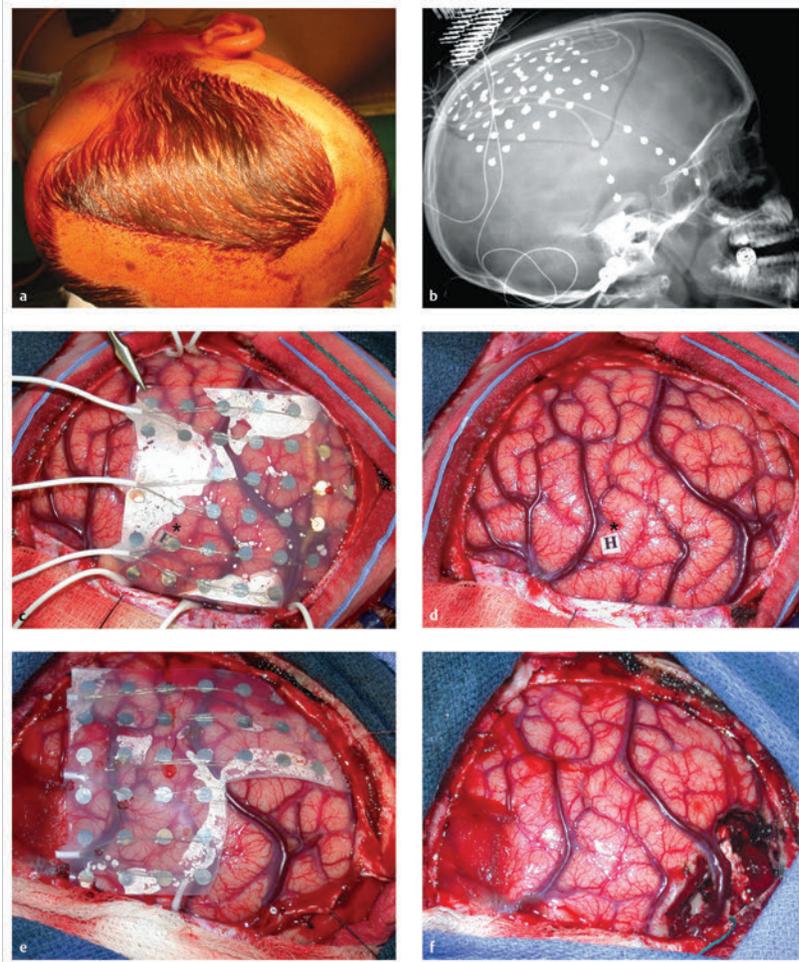


Fig. 73.3 Intraoperative photographs of a parietal lobe resection. (a) Intraoperative photograph showing surgical positioning to maximize cortical exposure for placement of the grids. A small strip of hair has been removed and the skin prepared for incision. The head is placed parallel to the floor. (b) Postoperative lateral plain radiograph revealing parietal placement of the grid and strip electrodes for ictal localization. The underlying craniotomy can be seen. (c) This photograph reveals the grid array over the affected cortical surface. The asterisk (*) represents the underlying hand motor cortex. (d) Image of the cortex with the grid array removed revealing the underlying mapped hand motor cortex. Asterisk (*) represents the hand motor cortex adjacent to the placed marker. Note the large cortical draining veins. (e) This photograph shows the grid array left in place and cut to reveal the underlying epileptogenic cortex. The wires have also been trimmed to facilitate exposure. (f) Resection bed following removal of the epileptogenic tissue. The large cortical draining vein has been preserved and hemostasis maintained.

iEEG monitoring in children, reports indicate that the rate of culture-positive infections is approximately 6%,¹²⁴ which is comparable with that for other cranial procedures.

The clinical care of patients who are candidates for iEEG requires special consideration. The use of valproate, which may limit platelet function and increase the risk for perioperative intracranial hemorrhage, must be limited and the patient switched to a new AED. Awake craniotomies in children are also limited because in most cases children are noncompliant¹²⁵ and cannot effectively communicate.¹²⁶ Neuroanesthesia may include the use of dexmedetomidine,¹²⁷ an α -agonist that can be titrated for awake-asleep periods to facilitate cortical mapping.³⁰ Of the children who undergo prolonged iEEG monitoring, 14% will not subsequently receive surgical resection. Children with preoperative normal neurologic examinations, multifocal regions of ictal onset, or involvement of a critical eloquent area may not undergo surgical resection.¹²⁸

A three-stage procedure has been described in which after the second resection, new subdural electrodes are left in place for a second period of extraoperative monitoring. Multistage epilepsy surgery may offer the benefit of identifying areas of incomplete resection, especially in cases of multifocal disease. This technique may decrease the need to take the patient back for an unplanned resection of epileptogenic tissue that is later discovered.¹²⁹ The elevated risk for infection and perioperative risks must be considered before this strategy is employed.

73.7.3 Disconnection Procedures

Posterior disconnections have also been described when epileptogenic tissue is identified in the temporoparieto-occipital regions. An anterior temporal lobectomy can be combined with disconnection of the parieto-occipital lobes by preserving the vein of Labbé and the sylvian vessels. The incision is started on the superior temporal gyrus (T1) and carried to the trigone.¹³⁰ The resection is then carried posteriorly to the postcentral gyrus and all the way to the vertex to reach the falx, while all white matter is transected. Forniceal connections are then sacrificed just anterior to the splenium to interrupt hippocampal output.¹³¹

73.7.4 Palliative Epilepsy Surgery

Although the primary goal of surgical intervention in ETLE is to obtain a seizure-free outcome, there are other meaningful outcomes that must be considered, such as reducing the seizure burden and the comorbidities associated with frequent seizure activity. Palliative epilepsy surgery has been developed, with several techniques focusing on just such outcomes when freedom from seizures is deemed unobtainable. The benefits of pursuing palliative surgical approaches are that AEDs can be titrated or changed to reduce the cumulative side-effect profile and that certain types of seizures, such as atonic drop attacks, that may be impairing a child's daily quality of life, can be eliminated.

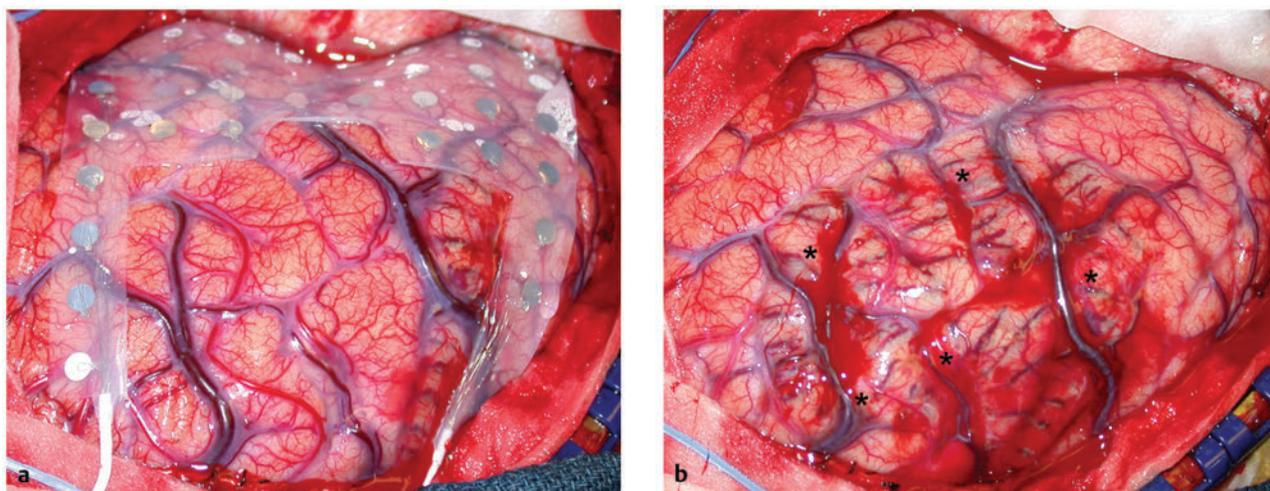


Fig. 73.4 Multiple subpial transections (MSTs) of affected cortex. (a) Intraoperative photograph revealing the affected cortex as determined by intraoperative electrocorticography. A portion of the grid array has been left in place to guide the MSTs. (b) Photograph of the same cortical region following the MSTs. The asterisks (*) mark the areas where MSTs were performed in eloquent cortical regions.

Multiple Subpial Transections

Lesions in primary visual, motor, or language cortex may prevent or limit surgical resection, thereby reducing the likelihood of seizure-free outcomes. When diagnostic approaches have identified epileptogenic lesions in eloquent cortex, MSTs can be utilized to disrupt the horizontal spread of epileptogenic activity between the vertically arranged functional units of cortex.¹³² If the horizontal fibers are disrupted with transverse incisions, seizure frequency can be reduced while normal neurologic function is preserved. Meta-analysis reveals that MSTs alone¹³³ may achieve seizure-free rates approaching 60 to 70%, depending upon the seizure subtype.¹³⁴ MSTs can be performed alone or in conjunction with lesionectomy, but their use may be correlated with poor control of seizure frequency.¹³⁵ In an international survey,⁴ MSTs were the most infrequently used technique in children with epilepsy (in 0.6% of pediatric epilepsy cases).

The location for MSTs is determined with intraoperative ECoG to identify areas of persistent epileptiform activity following surgical resection of adjacent cortex (► Fig. 73.4a). The application of bipolar electrocautery at 5-mm intervals along an involved gyrus is followed by a sharp incision in the pia mater. The instrument used is commonly a wire “knife” whose end is bent to a right angle with a length of 4 mm in order to span the gray matter.¹¹³ Sharp transection with the MST knife is carried out perpendicular to the gyrus and to a depth of 5 to 10 mm by drawing the tool back along the subpial surface. Cortical vessels are avoided during this procedure (► Fig. 73.4b). Ongoing ECoG confirms the absence of spike-wave activity and a reduction in epileptiform activity.¹³³

Complications arising from MSTs are reported in 19% of patients in whom the technique was used alone and in 23% of patients in whom it was combined with lesionectomy.¹³⁴ Deficits include transient hemiparesis, dysphagia, and other neurologic deficits related to the underlying cortical function. Eloquent cortical function is maintained as long as there is minimal damage to the neocortical columns and their vascular supply.^{32,136}

Recurrence rates for seizures following MSTs are elevated, at 18% in long-term follow-up studies.¹³⁷

Cortical Cooling

Finally, experimental models have led to the development of cortical cooling with Peltier devices, a technology similar to that used in polymerase chain reaction (PCR) machines. In experimental settings, animals have shown decreased seizure frequency and abortion of seizures when exposed to cortical cooling.¹³⁸ With histopathologic evidence that the underlying cortex has not been damaged, there is hope that this technology can be incorporated into clinical use for children with ETLE.¹³⁹

73.8 Common Pediatric Pathologies

ETLE can arise from a number of different pathologies in the pediatric population, most of which are associated with abnormalities in the progression of cortical maturation. Any disturbance in this well-orchestrated process can lead to the formation of epileptic foci throughout the pediatric brain. Pathologies encountered in pediatric epilepsy will vary greatly depending upon the age of the patient. Ninety percent of the surgical cases in infants will be hemispherectomies or multilobar resections as a consequence of their having multifocal cortical dysplasia, hemimegalencephaly, or Sturge-Weber syndrome.²⁷ In contrast, 65% of patients older than 10 years will undergo focal resections as a consequence of having tumors or FCD.

Based on the classification of MCDs, four major groups of diseases can be identified as potential causes of ETLE in children.⁶ Disorders in the first group result from abnormalities in neuronal and glial cell proliferation and include microcephalic states, lissencephalies, macrocephalic states like megalencephaly, cortical dysplasias with and without abnormal cells, and neoplastic lesions, such as gangliogliomas and gangliocytomas. Disorders in the next group result from abnormal neuronal migration and

include subcortical band and other heterotopias. Diseases giving rise to MCDs in the third group result from the dysregulation of corticogenesis and cortical organization and include polymicrogyria and schizencephalies. Finally, diseases in the fourth proposed group result from malformations of unspecified origin, including inborn errors of metabolism secondary to mitochondrial and peroxisomal disorders.

Additional etiologies of pediatric ETLE include neurocutaneous disorders, vascular and perinatal insults and infections leading to meningoencephalitis, trauma, and various other syndromes (see box “Common Etiologies of Pediatric ETLE in Children with Surgically Amenable Disease (p.962)”). Identifying the etiology of ETLE is essential because counseling can offer families insight into the risks for disease in additional offspring and can aid in identifying the potential clinical course associated with the particular pathology. As the study of human molecular genetics substantially improves our understanding of the genetic underpinnings of the various ETLEs, specific medications and therapies may be attempted to address the underlying genetic impairment resulting in epilepsy.

Common Etiologies of Pediatric Extratemporal Lobe Epilepsy

- Glial and neuronal proliferation or apoptosis disorders
 - Microcephalies
 - Macrocephalies
 - Hamartomas (tuberous sclerosis, hypothalamic hamartoma)
 - Hemimegalencephaly
 - Dysembryoplastic neuroepithelial tumor
 - Ganglioglioma
 - Gangliocytoma
- Neuronal migration disorders
 - Subcortical band heterotopia
 - Heterotopia
- Cortical disorganization disorders
 - Polymicrogyria
 - Schizencephaly
- Malformations not otherwise classified
 - Mitochondrial metabolic disorders
 - Peroxisomal disorders
- Other
 - Stroke
 - Trauma
 - Infection
- Various syndromes
 - Neurocutaneous (Sturge-Weber, neurofibromatosis)
 - Lennox-Gastaut
 - Rasmussen
 - West
 - Ohtahara
 - Hemiconvulsion–hemiplegia–epilepsy
 - Landau-Kleffner
 - Dravet
 - Panayiotopoulos

Note: Representative examples of each group are given, indicating the breadth of pathology seen in children with surgically amenable disease.

73.8.1 Focal Cortical Dysplasia

Since its first description in 1971, FCD has come to be recognized as the most common cause of intractable seizures in children, accounting for approximately 50% of cases in a surgical series.⁴ FCD is an area of malformed cortex that is frequently associated with epileptiform activity in children and has been classified into a three-tier system based on histopathology.¹⁴⁰ FCD type I is abnormal cortical lamination with abnormal radial and/or tangential layering effects. To identify FCD type I lesions, multiple neuroimaging modalities are necessary and range from volumetric or voxel-based analysis to FDG-PET. Despite advances in diagnostic imaging, cases of isolated FCD type I can be difficult to identify and are associated with worse seizure-free control.

Type II is subdivided according to the presence of cytologic abnormalities in addition to disrupted cortical lamination. Dysmorphic and enlarged neurons without balloon cells are found in type IIa, whereas type IIb has the hallmark eosinophilic balloon cells with large cell bodies. Patients who have type II FCD are usually younger at seizure onset and have an increased seizure burden in comparison with patients who have type I FCD. Preoperative studies of FCD with MR imaging may identify several areas of focal cortical malformation. FCD type IIb often presents with dyslamination, blurring of the gray matter–white matter junction, and thickened cortex that is identified on T2-weighted and FLAIR images. Type IIb presents with the “transmantle sign,” a radiographic feature in which white matter changes taper from the gyrus toward the ventricle along a sulcus. FCD type IIa, however, can be more difficult to identify on MR imaging. In addition, type IIb has a unique electrophysiologic signature on stereotactically placed depth electrodes for iEEG recordings. There is an absence of background activity, with high-amplitude fast spikes followed by high-amplitude slow waves. Finally, a recent classification has established type III FCD, which is associated with hippocampal sclerosis (type IIIa), with adjacent glial tumor (type IIIb), or with an associated injury acquired early in life (type IIIc). Resection of the focal pathology in FCD is the best predictor of postoperative seizure freedom.¹⁴¹ Both MR imaging and EEG findings improve complete resection and the opportunity for seizure-free outcome.

73.9 Outcomes

To standardize outcome reporting, Engel et al defined a classification system for the postoperative evaluation of patients.¹⁴² The scoring system is based on four main classes. Patients in class I have complete freedom from disabling seizures or only simple partial seizures remaining. Patients in class II have rare disabling seizures with more than 90% seizure freedom. Class III outcomes are seen as worthwhile improvement, with seizure reduction of more than 50%. Finally, patients in class IV have appreciable change in seizure frequency.

When compared with those who underwent resection for temporal lobe epilepsy, pediatric patients who had ETLE resections were reported by numerous groups to have significantly worse Engel outcomes.¹⁴³ Seventy-five percent of children with temporal lobe epilepsy were reported to have Engel class I or II outcomes, whereas only 50% of those with ETLE had class I or II

outcomes.⁵³ The inability of extensive diagnostic studies with invasive or noninvasive techniques to identify an underlying lesion or epileptogenic zone likely contributes to the decreased rates of seizure freedom in children with ETLE. As more modern series¹⁴⁴ of ETLE surgery have been reported,¹³⁵ the benefits of advances in neurophysiology are appreciated.¹⁴⁵ In a report in which iEEG monitoring was used, 60% of children with frontal lobe epilepsy were seizure-free following resections of tumors, FCD, or gliosis.¹⁴⁶ Seizure localization with scalp EEG can be challenging, with rapid propagation, and iEEG has helped to improve surgical outcomes.

Postoperative EEG studies may also help to predict outcomes following surgery; an acute seizure in the first postoperative week is associated with worse seizure-free outcomes.¹⁴⁷ Acute postoperative seizures occur in approximately 26% of patients with ETLE and should trigger additional diagnostic studies to identify the etiology of the residual epileptic activity. Seizures during this period may result from the surgical manipulation of tissue, infection, hemorrhage, metabolic derangements, altered anticonvulsant medication levels, and residual epileptogenic tissue. The presence of postoperative IEDs has a positive predictive value of 52% and a negative predictive value of 71% for lower seizure-free rates.¹⁴⁸ However, postoperative EEG studies should be used with caution in attempts to predict surgical outcome because inconsistent results can be caused by the heterogeneity of the seizure etiology, duration of follow-up, and patient population being investigated.

Recent meta-analytical data have indicated factors related to seizure outcome in pediatric ETLE in comparison with temporal lobe epilepsy.¹⁴⁹ There was a significant association between Engel outcome and seizure semiology, with better results seen in patients who had complex partial seizures. Many authors have reported series in which preoperative imaging identified a lesion¹⁵⁰ and removal of the lesion was associated with a higher rate of success than could be achieved with a diffuse process or nonlocalizable lesion.¹⁴¹ Meta-analytical data¹⁵⁰ also confirm that a recognizable lesion on MR imaging is significantly associated with a better Engel I outcome.⁵⁷ Improved outcomes in cases with identified lesions are attributed to a possible shorter duration of epilepsy than in cases in which lesions were not localized, so that additional diagnostic investigations were required. MEG concordance with preoperative EEG localization of epileptogenic zones predicts better seizure-free outcomes.⁹⁵

Also impacting outcomes is the etiology of the seizures. For example, tumors at extratemporal locations are associated with a higher percentage of Engel class I and class II outcomes. FCDs have a better prognosis than nonfocal lesions.¹⁴⁹ Certain etiologies, such as meningoencephalitis and perinatal insults, may result in multifocal epilepsy, making it more challenging to obtain seizure freedom in these cases. Complete resection of ictal zones defined on MR imaging or EEG is significantly correlated with improved seizure-free rates.¹⁴¹ Confirmation of a lesion on pathology is also predictive of an Engel I outcome.¹⁵⁰

Neurocognitive studies looking at cases of ETLE and neurocognitive outcomes report that duration of epilepsy, age at seizure onset, and etiology are independently associated with lower IQs in children. Surgery for the various etiologies did not impact cognitive outcome.¹⁵¹ A child's outcome after these and other surgical procedures can be measured in terms of a

development quotient (DQ). The DQ takes into account the child's developmental performance in areas of cognition, intellect,¹⁵² and motor and other skills at his or her developmental age (DA). The DA can then be divided by the chronological age to determine the DQ. Patients with higher DQs preoperatively are found to have surgical outcomes better than those of children with lower DQs.^{25,153} Patients who undergo surgery as infants show the greatest improvement in DQ after surgery. The negative impact of persistent ETLE in children can therefore be appreciated by their poorer neurocognitive outcomes and decreased likelihood of recovery to appropriate developmental milestones in comparison with control patients.⁹⁸ Early surgery also improves behavioral disorders and psychosocial outcomes in certain cases of ETLE.^{154–156}

The location of seizures also appears to influence seizure outcomes. Meta-analysis of outcomes data from various ETLE surgical cases reveals a tendency for frontal lobe resections to have worse outcomes than posterior cerebral resections.¹⁴⁹ The worse outcomes in ETLE, in comparison with those in temporal lobe epilepsy, result from the involvement of eloquent cortex functioning in speech, language, sensorimotor processing, and vision.¹⁵⁰ It is not possible to resect large sections of cortex to eliminate an epileptogenic region, so that epileptic tissue is left behind to continue seizure propagation. Despite concern regarding the outcomes of surgery involving sensorimotor cortex, seizure freedom can be obtained in these cases.³² Approximately 77% of patients who underwent surgery for rolandic cortex seizures had an Engel I or II outcome, with minimal neurologic deficits at follow-up evaluation.

73.9.1 Frontal Lobe

Frontal lobe epilepsy is the most common ETLE in children and also has the worst reported seizure-free outcomes; this finding is related to several variables.¹⁵⁰ Seizure recurrence following surgery is more likely when patients have an MR-negative MCD, generalized or nonlocalized EEG patterns, acute postoperative seizures, or incomplete resections. Seizure-free rates 5 years following frontal lobectomy may be as low as 30%, and as low as 15% if the aforementioned negative prognostic factors are present.¹⁵⁷ In other reports, seizure-free rates vary from 50 to 65%^{8,158} in cases of frontal lobe epilepsy treated by lesionectomy. Complications of resection or of ongoing seizures can result in a frontal lobe syndrome of attention deficits, limited motor skills, behavioral abnormalities, and subtle changes in executive functioning. These results may be transient or, if they are related to persistent seizures, controlled with medication.^{159,160}

Neurocognitive outcomes following frontal lobe seizures can be difficult to assess because the degree of severity may not be fully appreciated until adolescence. Nevertheless, several studies have investigated the neurocognitive effects of ETLE surgery. Postoperative evaluation in children undergoing surgical intervention for epilepsy found that attention, as well as short- and long-term memory, were improved in comparison with a control group that had no surgery, although no significant differences in executive functions were noted.¹⁶⁰ Of interest, the benefits seen did not depend upon achievement of an Engel I outcome. Laterality of the surgery may impact outcomes, with left-sided resections causing word fluency problems whereas

right-sided surgery impairs fluency.¹⁶¹ The Engel I outcome correlates with improvement in short-term memory in postoperative patients. When the outcomes of children with frontal or temporal lobe epilepsy are compared, the children with frontal lobe seizures may have a decline in IQ postoperatively and a greater impairment in motor coordination, yet greater improvement in behavioral abnormalities.^{32,161,162}

73.9.2 Parietal Lobe

Parietal seizures account for the lowest percentage of pediatric epileptogenic activity, and the reported outcomes of children with parietal seizures are frequently linked to those of patients with seizures of occipital origin. Parietal lobe resections account for an estimated 4 to 14% of ETLE cases.¹⁶³ In mixed series of patients with epilepsy located in the posterior cortex, 40 to 72% had Engel I or II outcomes, with an estimated 35% having visual field defects postoperatively.^{37,163} Complications also included transient hemiparesis, aphasia, and somatosensory defects.³⁷ In addition, postoperative Gerstmann syndrome, with acalculia, right-left disorientation, finger agnosia, and agraphia, has been described after parietal lobe resections.¹⁶³ With limited surgical volume and experience in this area, the authors recommend tailored cortical resection based upon intraoperative ECoG or iEEG data.¹⁶³ Proximity to eloquent cortex precludes the complete resection of epileptogenic tissue in this region, and few diagnostic procedures have been linked to improved seizure-free outcomes for this location.³⁷ MSTs in the adjacent eloquent brain may be required to decrease seizure frequency or eliminate seizures.¹⁶³ In one of the few reports on neurocognitive outcomes in children who underwent parietal lobe epilepsy surgery, improvements in behavior and attention were identified, whereas cognitive functions remained unchanged.³⁵

73.9.3 Occipital Lobe

Extensive studies have reported outcomes following occipital surgery. It is estimated that upward of 60 to 68% of patients will have satisfactory Engel class I or II outcomes.^{43,164} Seizure outcome may depend on the concordance of diagnostic studies to localize the ictal focus.⁴³ MEG aids the resection of epileptogenic tissue, and the detection of dipoles in the contralateral occipital lobe³⁹ is associated with improved outcomes. Seizure outcome may also be related to a shorter duration of epilepsy.³⁶ A significant portion of patients will have a new or worsened visual field deficit after surgery, with 25 to 80% of patients in some series experiencing visual field changes.^{36,43} Some studies suggest that visual processing may be reorganized following surgery and that deficits may lessen as a consequence of neural plasticity.¹⁶⁵ The potential for recovery may be limited as a result of the early maturation of the posterior cortex. When patients are evaluated after the surgical resection of parietal or occipital lobe seizure foci, the recovery of visual perceptual cognition is limited, and it is possible that earlier surgery to reduce the degree of damage done to surrounding cortical circuitry can optimize cognitive outcomes in children. In the few reports of neurocognitive outcomes in patients with parietal and occipital lobe epilepsy, surgical resection appeared to improve verbal IQ more than performance IQ.¹⁶⁶ Although the numbers may be limited, 80% of the children achieved normal schooling levels.

Persistent deficits existed, however, in visual attention, object and facial recognition, and reading speed, which are functions subserved by the occipital and parietal regions of the cortex.

73.9.4 Neurocognitive Outcomes

Traditionally, children with behavioral issues or mental retardation have been viewed as less likely surgical candidates because these comorbidities are associated with a poorer prognosis.¹⁶⁷ A low preoperative IQ has also been reported as indicative of a poor surgical outcome because it may be related to diffuse cortical involvement.¹⁶⁸ As more contemporary studies expand the surgical indications for pediatric ETLE and the selection criteria for patients, the results hold promise of the inclusion of patients with lower IQs. Nearly 50% of children with an IQ below 70 had seizure freedom, whereas 68% of children with less severe retardation achieved seizure freedom.¹⁶⁹ Additional studies report seizure-free rates of 22 to 37% in children with an IQ below 70.¹⁷⁰ Although a lower IQ is a poor prognostic factor, there are children who can still benefit from surgical intervention. Persistent failures in patients with lower IQs may be attributable to a higher incidence of mixed seizures and diffuse cortical involvement. Despite these factors, palliative treatment options of corpus callosotomy and vagal nerve stimulation remain available, the benefits of which may not be seen until 1 to 2 years postoperatively.¹⁷¹

Neurocognitive outcome studies in children are needed to acquire future insight because the prevalence rates of behavioral, emotional, and socialization deficits are higher in children with epilepsy than in control populations.¹⁷² Despite reports in the adult literature, there remains a gap in the standardized reporting of outcomes in studies of pediatric ETLE.¹⁷³ One study that included children with ETLE revealed that the social interaction scores of children who had surgery improved, and that improvements continued to occur up to 2 years postoperatively.¹⁷² The greatest gains were seen in children with Engel I outcomes. Improvement may derive from a number of factors, including increased socialization with peers, parental acceptance of a seizure-free state, and recovery or plasticity in response to resolving IEDs. Although children are reported to have some improvement in outcome studies, they continue to experience deficits compared with controls.¹⁴ Neurocognitive abnormalities may persist as a result of a child's environment, which may include the continued use of anticonvulsant medications, persistent seizures if an Engel I outcome is not achieved, and persistent social stigmatization in classroom environments.¹⁷⁴

Although seizure freedom is the ultimate goal in pediatric ETLE, there are children possibly at risk for behavioral problems or poor performance who might benefit from the continued role of epilepsy surgery to prevent cognitive and developmental decline.¹⁷⁵ Defining successful outcomes when seizure freedom is not a realistic goal is a challenge for neurosurgeons treating pediatric ETLE. There is an expanding awareness that a reduction in the seizure burden, a stabilization of neurocognitive function, and a decrease in the overall requirement for medications may be secondary outcomes that significantly improve a child's quality of life and that of his or her family.¹⁷⁶ A case-by-case analysis is therefore warranted in a multidisciplinary setting to determine likely outcomes with the aforementioned

treatment approaches and to determine which cost–benefit analysis best suits an individual patient.

Throughout the literature, there is a lack of unanimity regarding preoperative assessment, diagnostic techniques, surgical techniques, and measures of outcomes in pediatric ETLE. Multicenter trials to pool patient data and coordinate clinical care strategies for these patients might be of benefit by clearly illuminating the paths toward improved outcomes and eliminating regional or institutional biases. Established centers have clearly paved the way for the multidisciplinary treatment of ETLE; however, future success requires that these centers coordinate their cost-effective and safe improvements in clinical care.

73.10 Conclusion

Extratemporal cortical resections play a large role in the treatment of medically refractory pediatric epilepsy, whereas adult epilepsy surgery commonly involves temporal resections. Two-stage procedures with invasive subdural and depth intracranial electrode arrays allow the localization of ictal onset and mapping of eloquent functions in nonlesional cases; they also may be helpful in lesional cases with discordant presurgical diagnostic data or a seizure onset near or within eloquent cortex. Although the developing brain is vulnerable to ongoing or re-mitting seizures that can stunt cognitive development, it also has a tremendous amount of plasticity that can result in surprisingly good neurologic recovery, even when eloquent cortex must be sacrificed. Ongoing advances in anatomical and metabolic imaging, functional localization, and surgical techniques, as well as improvements in patient selection and an increasing recognition of the value of neurocognitive testing and follow-up, are resulting in improved outcomes for an increasingly large number of children over time. All children with refractory epilepsy should be evaluated at a comprehensive epilepsy center to determine if they might benefit from the ever-increasing stable of nonsurgical and surgical options that are now available.

Pearls

- Multidisciplinary teams offer expertise and familiarity with a host of diverse pediatric extratemporal lobe etiologies.
- All children with medically refractory epilepsy should be referred to a pediatric epilepsy center for evaluation.
- A comprehensive presurgical consultation with patients and families helps to set realistic expectations and goals.
- Staged procedures with subdural grids and electrodes improve ictal localization when MR imaging and other preoperative studies are unsuccessful in identifying a lesion. Detailed ictal localization and functional cortical mapping are significant advantages seen with two-stage procedures.
- Neural plasticity in younger children can substantially mitigate early postoperative neurologic deficits.
- Maximal concordance between diagnostic studies may yield the best rates of seizure freedom.
- A more favorable prognosis can be expected after extratemporal resections when surgery is lesional, the ictal onset is focal, the diagnostic studies are concordant, and wide resections are performed.

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74 Nonresective and Neuromodulatory Treatments of Refractory Epilepsy

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As many as 10 to 40% of pediatric patients with epilepsy have intractable seizures, despite the use of multiple antiepileptic agents.¹⁻³ Seizure control is especially important in the pediatric population because persistent seizures can profoundly impair cognitive and psychosocial development.^{4,5} In these patients, surgical intervention can be offered as an alternative means of seizure control.

Epilepsy is a diverse entity caused by a range of distinct pathologies. For this reason, multiple surgical interventions have emerged for the treatment of various disease processes. Beginning with Horsley's excision of neocortical tissue for focal motor seizures in 1886⁶ and the pioneering work of Foerster, Penfield, Jasper, and others, epilepsy surgeries have classically been resection procedures with the goal of removing or ablating epileptogenic tissue. These procedures include both focal resection (lesionectomy) when discrete anatomical lesions like neoplasms and vascular anomalies can be identified, and wider excisions (corticectomy, lobectomy, hemispherectomy) when the underlying pathology is more diffuse, as in malformations of cortical development and mesial temporal lobe sclerosis. The goal of resection procedures is curative, with the hope that removal of a presumed primary epileptogenic focus will prevent further seizures. These strategies of focal resection and their application in children are discussed in other chapters.

In many patients, resection is not a viable option, either because there is no clearly identifiable seizure focus, there are multiple diffuse epileptogenic foci, or an epileptogenic focus exists in nonresectable eloquent cortex. In such cases, nonresective interventions should be considered. Instead of the resection of epileptogenic tissue, the goal of these interventions is to modulate the existing circuits to control seizure initiation, propagation, and/or generalization. Nonresective treatments are generally palliative rather than curative, with the intended goal of reducing the frequency or severity of seizures. Two subtypes of procedures fall into this category of neuromodulation: disconnection procedures and neurostimulation. Disconnection procedures transect afferent and efferent fibers in an attempt to functionally isolate surrounding epileptogenic tissue—either directly or indirectly interrupting pathways that mediate excitation and seizure propagation from a primary focus, or disrupting more complex dynamics, such as subcortically mediated synchronization or network-level coupling, to prevent the generalization of pathologic synchronous neural activity. The mechanism of action of neurostimulation procedures is more complex. Generally speaking, an electrical stimulus is initiated to “modulate,” either directly or indirectly, through the excitation of excitatory or inhibitory pathways of the neural networks involved in epileptogenesis. We review here the most common nonresective neurosurgical strategies for intractable epilepsy, with a particular focus on corpus callosotomy and vagus nerve stimulation.

74.1 Disconnection Procedures for the Isolation of Epileptogenic Tissue

74.1.1 Multiple Subpial Transections

Multiple subpial transections (MSTs) were introduced by Morrell and colleagues for medically refractory partial epilepsy originating in eloquent regions of neocortex.⁷ The rationale for MSTs is based on the concept that normal neurophysiologic function relies primarily on vertically oriented fibers, independently of the lateral propagation of seizure activity. Transecting the cortex in the horizontal plane disrupts seizure spread while sparing normal function. Multiple retrospective studies have demonstrated that MSTs are safe and efficacious⁸⁻¹³; however, this has not yet been validated by a prospective trial.

To create MSTs, a fine microdissection device is introduced through the pia and is used to make vertical transections oriented perpendicularly to the long axis of a gyrus, with parallel transections repeated at approximately 5-mm intervals across the epileptogenic region. Postsurgical results reveal a generally excellent seizure response (60 to 70% patients achieved >95% reduction in seizure frequency in a recent international meta-analysis); the comparable responses for MSTs alone and the combination of MSTs plus resection in partial seizures validate the disconnection paradigm as a viable means of seizure control.¹⁴

74.1.2 Functional Hemispherectomy

Functional hemispherectomy (hemispherotomy) is analogous to MSTs in that it attempts to circumscribe and isolate an epileptogenic focus; however, the target region is an entire hemisphere rather than a single lesion, and the isolated neural circuits are completely disconnected from the rest of the brain. This procedure and several variants are modifications of the original hemispherectomy procedure,¹⁵ with the frontal and occipital poles left intact but disconnected to avoid the superficial cerebral hemosiderosis related to hemorrhage into the extended resection cavity.¹⁶ Functional hemispherectomy, which is discussed in Chapter 75, is different from the other disconnection procedures considered here in that there is no intention of preserving the function of the neurons left behind but disconnected.

74.1.3 Corpus Callosotomy

Division of the corpus callosum to prevent seizure generalization is the other major type of neurosurgical disconnection procedure. Corpus callosotomy has been shown to be safe and effective, with the greatest benefit for patients with intractable drop attacks and/or generalized tonic-clonic seizures.¹⁷⁻¹⁹

Dandy initially reported the feasibility of operative corpus callosum division after using this maneuver for pineal tumor resections.²⁰

Disconnection of the cerebral hemispheres to treat intractable seizures was then proposed by Van Wagenen and Herren soon thereafter,²¹ contemporaneously with pioneering work by Erickson on the effect of callosotomy on seizure propagation in the monkey.²² Although additional midline structures, including the interhemispheric commissures, massa intermedia, and fornix, have been the targets of disconnection procedures, there is no clear benefit beyond that of corpus callosotomy alone. Today, understanding is evolving about both the functional implications of corpus callosum division and the possible mechanisms of seizure control with corpus callosotomy.

Corpus Callosum: Anatomy and Function

The corpus callosum is the largest commissural connection in the human brain, consisting of an estimated 200 million interhemispheric fibers between primarily homologous areas of neocortex.²³ Most callosal fibers connect higher-order association areas, with only minimal callosal projections observed between primary motor or sensory cortices. Although the anatomical organization of the callosal fiber tracts is now well-established, the mechanisms mediating the transfer of information are still a topic of debate.²⁴ Many studies support an excitatory role, in which the corpus callosum allows the interhemispheric integration of information. Others suggest that callosal fibers impose an inhibitory effect on the opposite hemisphere, leading to increased lateralization and allowing more efficient processing.^{25,26}

Anatomically, the corpus callosum demonstrates a heterogeneity of fiber composition and connectivity that underlies its various physiologic functions. Despite their relatively sparse representation in the callosum, connections between primary and secondary sensorimotor regions comprise the majority of large-diameter myelinated callosal fibers in the primate brain.^{23,27} This distribution of fast-conducting fibers is consistent with hypotheses that fast interhemispheric processing via the corpus callosum mediates certain midline fusion tasks, such as central vision, depth perception, binaural sound localization, and aspects of bimanual coordination.²⁸⁻³¹ In contrast, interhemispheric connections between higher-order neocortical regions, such as the prefrontal cortex and extrastriate visual cortex, consist primarily of small-diameter unmyelinated fibers. Such slow-conducting fibers have been theorized to mediate the integration of more processed information between associative cortices.²⁷ There is also a generally rostral-to-caudal topography of callosal fibers corresponding roughly to the neocortical regions they interconnect: prefrontal fibers in the rostrum and genu; motor, somatosensory, superior temporal, and parietal fibers in the body; and inferior temporal and visual fibers in the splenium.^{32,33} Neurotracing studies suggest that the vast majority of these interhemispheric connections are homotopic, but heterotopic callosal fibers mediating interhemispheric parallel processing between different associative areas may also play a role.³⁴ Likely the addition of tractography with diffusion tensor imaging and improved functional imaging and electrophysiologic modalities will help to elucidate the functional aspects, circuitry, and networks delivered in communication through the corpus callosum.

Various animal and human models have been studied to better elucidate the function of the corpus callosum. Experiments in callosotomized animals first established a role for the corpus callosum in the somatosensory transmission of information between the hemispheres.³⁵ However, its involvement in more complex cognitive function required direct evaluation in human models and human pathologic conditions.

Congenital callosal agenesis has been extensively studied and has contributed to our current understanding of callosal function.^{36,37} However, these studies should be interpreted with caution because patients with congenital callosal agenesis often have other structural abnormalities (e.g., absence of the anterior commissure and hippocampal commissure).³⁸ Furthermore, with congenital absence of the callosum, reorganization and functional compensation likely occur, given the neural plasticity of the developing brain.³⁹⁻⁴¹ In contrast, the ability of the brain to compensate for lesions acquired postnatally is more limited.

The most meaningful functional data have been generated in human patients with a postsurgical split brain. Over the past 40 years, a growing neuropsychological literature has accumulated describing the effects of partial or complete callosotomy in patients with intractable epilepsy. In the cognitive nomenclature, the condition resulting from the callosotomy was termed *split brain*.⁴²⁻⁴⁴ The varying deficits and degrees of impairment seen after callosotomy indicate the subtle and diverse nature of callosal function. A characteristic acute neurologic syndrome occurs in the first few postoperative days and includes most frequently mutism as well as nondominant arm and leg apraxia, bilateral Babinski signs, and urinary incontinence.^{45,46} These complications are almost always transient (although left-sided apraxia can persist for weeks or in rare cases be permanent) and may result from intraoperative retraction and manipulation rather than callosal division.

Most of the persisting deficits following callosotomy involve the incomplete integration of information processing across hemispheres, often referred to in aggregate as the disconnection syndrome.⁴⁷ In general, these deficits are subtle, and controlled neuropsychological testing is often required to elicit them. There is limited interhemispheric transfer of unilaterally presented perceptual information, such as visual and shape information. After callosotomy, patients also show deficits in the temporal coupling of continuous (but not discrete) bimanual movements,²⁹ as well as difficulty in learning new tasks requiring bimanual cooperation.⁴⁸ However, previously learned bimanual tasks, such as playing the piano and tying shoelaces, are preserved, suggesting a callosal role in the initial integration of complex motor tasks before eventual transfer to subcortical and cerebellar structures. This is consistent with human studies showing interregional and interhemispheric coherence of electroencephalographic (EEG) signals across premotor and sensorimotor regions during the acquisition of bimanual tasks.⁴⁹ Language processing also exhibits deficits after callosotomy, which follows from the strong tendency of the human brain for lateralized language dominance. Images projected to the language-dominant left hemisphere (right visual field) can be easily described but cannot be verbalized when they are projected to the nondominant hemisphere despite their accurate reporting via nonverbal means (pointing).

Although many models support a transcallosal excitatory integration of information, there is evidence that some callosal

function may be inhibitory in nature. Activation of the motor cortex by a conditioning stimulus or direct electrical or transcranial magnetic stimulation causes inhibition of the contralateral motor cortex in animals and humans, likely via a transcallosally mediated activation of local inhibitory interneurons.^{50–52} After callosotomy, the normally unitary attention system can function as individual attentional processes,^{53,54} indicating a crucial role for the callosum in generating an integrated visuospatial attention system. Dual attentional processes may be prevented by interhemispheric inhibition in the normal brain, and the corpus callosum may have an integral role in generating selective attention. Tonic inhibitory processes are important to consider because disconnection procedures can produce a deafening of external inhibition to a region, which is a possible mechanism behind the occurrence of postoperative seizures.

Perhaps the most dramatic complication of callosotomy is the alien hand syndrome, which represents a disruption of perceived conscious will and volition.⁵⁵ Originally described by Goldstein in 1908 and further characterized by Akelaitis in 1945, patients with alien hand syndrome experience the subjective feeling of an upper limb performing complex motor acts outside their own volitional control.⁵⁶ In addition to the striking intermanual conflict that most vividly demonstrates the syndrome, other signs of alien hand syndrome include automatic mirror movements of the unaffected hand, enabling synkinesis, grasp reflex, magnetic apraxia or impulsive groping, and utilization behavior. Alien hand syndrome can be divided into cases arising from callosal pathology or unilateral lesions of the cortex, in which the “alien” hand is always contralateral to the lesion. In the “callosal” subtype, alien hand syndrome results from surgical transection, each with a signature symptomatology that results from damage to distinct anatomical structures.⁵⁷ The subtype of “callosal” alien hand syndrome results from surgical transection of the anterior corpus callosum or ischemia or rupture in the anterior cerebral artery circulation, presumably affecting fibers between premotor and motor areas. This subtype typically manifests as disrupted volitional control of the nondominant left hand. Although a relatively rare complication of callosotomy, the alien hand syndrome suggests that the corpus callosum participates in the construction of a unitary perception of “conscious will” by integrating either the performance of volitional action or the subjective perception of such behavior across hemispheres.

Corpus Callosotomy: Mechanism of Seizure Prevention

The goal of corpus callosotomy is the palliative treatment of intractable generalized seizures, but the physiologic mechanism of seizure control produced by the division of callosal fibers remains unclear. The initial rationale behind callosotomy for seizure control was that the interruption of transcallosal pathways would prevent interhemispheric synaptic activation and seizure propagation. However, more recent evidence suggests that the callosal role in epileptogenesis may be more complex. In some studies of EEG changes after callosotomy, preoperative bilaterally synchronous epileptiform discharges are transformed into primarily lateralized or asynchronous ones, suggesting a callosally mediated propagation of seizure activity from one hemisphere to another.^{58–60} However, other evidence supports a

mechanism involving an overall decrease in cortical epileptogenicity rather than an interruption of propagation pathways; callosotomy can produce a reduction in seizure severity and frequency without a transformation from generalized to partial seizures or, in some cases, complete suppression of seizure activity.^{14,58,61,62} Furthermore, in an intraoperative study of callosal compound action potentials and bilateral spike-and-wave discharges in epileptic patients, interhemispheric delay times were often less than the minimum axonal conduction time (approximately 20 milliseconds), and callosal compound action potentials peaked after their associated spike-and-wave complexes.⁶³

In addition to the direct transfer of synchronous seizure activity, other mechanisms of corpus callosum-mediated modulation of epileptogenesis have been proposed. One hypothesis is that both hemispheres are capable of generating epileptiform discharges and that the corpus callosum provides a pathway for the synchronization rather than the transfer of activity.⁶⁴ Consistent with facilitation via the corpus callosum, repetitive transcallosal volleys at 5 to 20 Hz enhance cortical reactivity as measured by thalamocortical responses in a rat model, an effect suppressed by callosotomy.⁶⁵ It should be noted that callosal pathways are not required for seizure generalization; patients with Aicardi syndrome have congenital agenesis of the corpus callosum yet exhibit infantile spasms in addition to ocular abnormalities and mental retardation.⁶⁶ In these patients, callosal pathways cannot mediate the propagation of synchronous activity from a lateralized focus, suggesting that seizure generalization must occur via other interhemispheric or subcortical tracts. From a wealth of animal studies, it appears that cortical and thalamic networks involved in physiologic sleep oscillations are critical in generating the spike-and-wave and polyspike-and-wave complexes seen in certain generalized epilepsies, such as absence epilepsy and Lennox-Gastaut syndrome.⁶⁷ A growing understanding of the behavior of interconnected networks indicates that the dynamic, oscillatory behavior of such systems is dependent on their topology, scale, and connectivity.⁶⁸ The corpus callosum may comprise critical internodal connections of hemispheric thalamocortical circuits that provide the necessary dynamic system to generate generalized synchronous ictal activity.

Corpus Callosotomy: Outcomes

Corpus callosotomy has been demonstrated to be effective in the treatment of generalized seizures since as early as 1940.¹⁷ Multiple retrospective series show a reduction of generalized seizures after corpus callosotomy, with response rates ranging from 56 to 100%.^{61,69–72} The best and most consistent responses are seen in patients with drop attack seizures of tonic, atonic, or mixed type, with response rates approaching 100% in some studies.^{18,71,73,74} Similar response rates are seen in pediatric series,^{69,75,76} and callosotomy reduces medically refractory seizures in specific pediatric epilepsies such as the West and Lennox-Gastaut syndromes.⁷⁷ In pediatric cases, an examination of parental satisfaction showed a high level of reported satisfaction with surgical outcome (88%), although interestingly satisfaction was not strongly correlated with measured seizure reduction and might have been related to behavioral changes, such as improved alertness and responsiveness.⁷⁸ Reduction in seizure

frequency is also correlated with perceived changes in quality of life, with improvements in self-care, family life, and school performance.⁷⁹

Although the efficacy of corpus callosotomy for drop attacks is generally well accepted, the factors that contribute to a favorable outcome have been a topic of debate. There has been significant variation in the extent of callosal division used to achieve seizure control. Several studies have demonstrated that total corpus callosotomy is more efficacious and durable than partial divisions in the treatment of drop attacks.^{17,18,70,71,80–82} In general, better results are achieved with greater extents of resection, and often clinical algorithms can be developed for recommending a complete callosotomy in children who have severe underlying cognitive dysfunction or language impairment. Partial callosotomy limited to the anterior two-thirds of the callosum can provide some degree of palliation in children with good cognition and language as a first stage, but incremental benefit can still be gained with the conversion of partial procedures to total divisions if seizures continue.^{70,77} Recognition of an increased risk for disconnection syndrome after the disruption of posterior callosal fibers, either alone or as part of total callosotomy,⁷² led to the development of a two-stage procedure in which an initial anterior callosotomy is followed by a 6- to 12-month evaluation period to determine effectiveness before optional conversion to total resection.⁷⁰ In terms of reduction of seizures, there are no observed differences between children and adults, and the outcome of either anterior or total callosotomy is not related to age at the time of surgery. Efforts to identify EEG predictors of responsiveness suggest that lateralized changes in interictal EEG can predict a good outcome of callosotomy,⁷¹ although specific patterns of ictal EEG activity may be a stronger prognostic factor.⁸³ Other factors that may portend a favorable outcome include the absence of abnormality on magnetic resonance (MR) imaging and the absence of identified seizure etiology.⁸⁴

Significant adverse effects are relatively rare with callosotomy, and standard neuropsychological and psychosocial assessments generally reveal little change compared with the pre-morbid condition.⁴⁵ A precise characterization of neuropsychological effects is difficult; many patients have preexisting developmental delay, frequent seizures, and multiple antiepileptic drug regimens, and effective seizure control often can improve testing results. A characteristic acute postoperative neurologic syndrome is observed with mutism, nondominant arm and leg apraxia, bilateral Babinski signs, and urinary incontinence.^{45,46} These complications are almost always transient, with the mutism resolving typically within several weeks, and evidence suggests that intraoperative retraction and manipulation, rather than callosal division, may be the cause.

Permanent side effects of callosotomy are relatively rare, with weakness or apraxia and impairment of language and behavior occurring in 8% of partial and 12% of total callosotomies.⁸⁵ After callosotomy, dysphasia is seen specifically in patients with mixed or crossed cerebral dominance, in whom the language-dominant hemisphere does not control the dominant hand⁸⁶; specifically, dysgraphia and dysphasia were seen in crossed-dominant right-handed patients, and dysgraphia alone was seen in crossed-dominant left-handed patients. Sensory disconnection resulting from the division of posterior callosal fibers is well documented, but the effects are subtle, and controlled

neuropsychological testing is often required to identify it (see above). Disruption of the interhemispheric integration of motor information makes it more difficult for patients who have undergone a callosotomy to learn new bimanual tasks,⁴⁸ but previously acquired bimanual tasks remain intact. Memory deficits are noted in a small subset of cases and may represent either preexisting extracallosal damage to structures like the fornix or extensive posterior callosal sections affecting the hippocampal commissures.^{87–89}

Corpus Callosotomy: Surgical Technique

Anterior callosotomy and single-stage complete corpus callosotomy are performed with the patient under general anesthesia. The patient is in the supine position, with the head elevated and very slightly flexed. Typically, we prefer a simple linear incision 2.5 cm in front of the coronal suture, extending from 3 cm to the left of midline to 7 cm to the right of midline, directly perpendicular to the midsagittal line (► Fig. 74.1). Two bur holes are placed right on the midline. One is at the bregma, the confluence of the coronal and sagittal sutures, or no more than 1 cm posterior to this point. The other is placed 5 cm anterior to the bregma, again directly at or just left of midline. To achieve adequate midline visualization along the corpus callosum, it is necessary that the bone flap come exactly to the midline or even slightly to the left of midline. The careful placement of bur holes directly over the sagittal sinus has proved to be a safe practice, but to avoid potential injury or any difficulty with midline visualization, the authors place the bur holes and the edge of the craniotomy slightly to the *left* of the sinus to avoid obstruction of the view by overhanging bone or injury to the sinus. A trapezoidal or D-shaped craniotomy that is 5 cm long is made with a high-speed drill.

The dural opening needs to be only 1.5 to 2 cm from the edge of the sagittal sinus and parallel to it. There are often bridging veins at the level of the coronal suture that require care in preservation as this dural opening is made. Venous lakes in the region also sometimes have to be oversewn. Although an experienced operator can visualize the entire corpus callosum through a smaller bone opening, we prefer approximately 5 cm of exposure here anterior to the coronal suture to provide flexibility in circumventing any bridging veins. Careful analysis of the vascular anatomy on MR imaging can be helpful in preparing for venous structures that may be encountered.

After the dura is opened, the right frontal lobe is gently retracted away from the falx under the microscope. Fixed retraction is avoided on the brain itself but can be applied to the falx side if necessary. There are occasionally significant arachnoidal adhesions, and below the lower limit of the falx there are almost always adhesions between the two cingulate gyri. Microscopic dissection is used to divide the arachnoidal adhesions. It is important not to mistake the callosal marginal arteries for the pericallosal arteries and therefore mistake cingulate gyrus for corpus callosum. The corpus callosum is significantly whiter and smoother than the cingulate gyrus, and generally one or both pericallosal arteries come into view at the same time as the corpus callosum.

Next begins the phase of dissecting between the two pericallosal arteries to expose the corpus callosum over the entire length of the needed visualization. Usually, there is no doubt

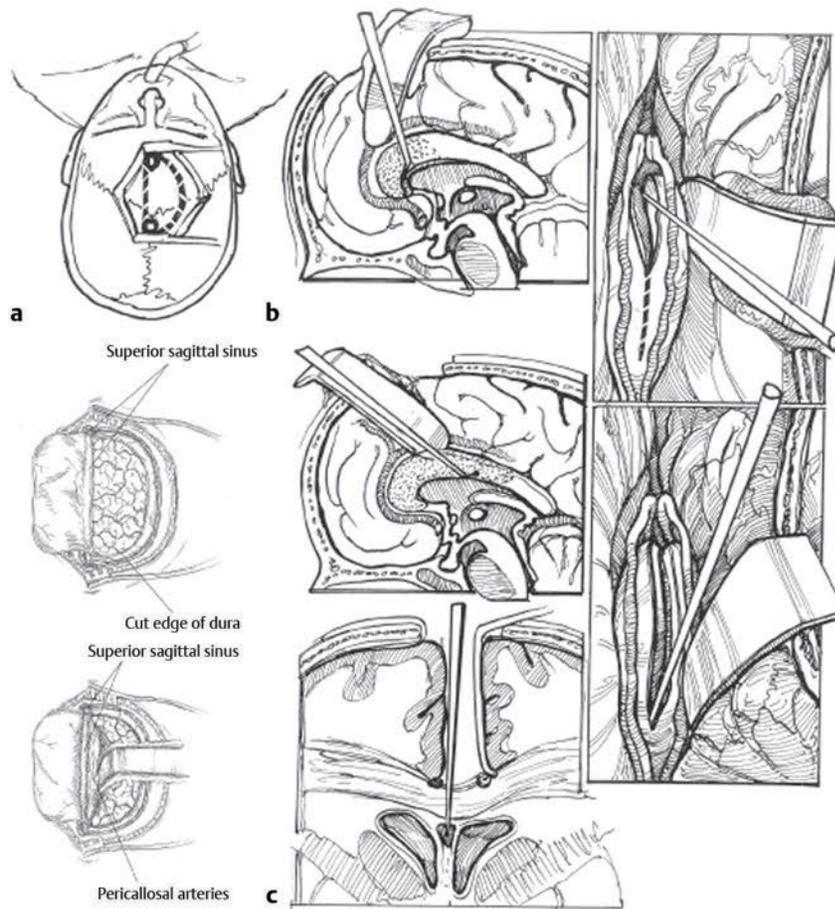


Fig. 74.1 (a) The child is positioned with the neck slightly flexed and the forehead toward the ceiling. A straight coronal incision 3 cm in front of the coronal suture permits a tight-shaped skull exposure. The craniotomy, in the shape of a large letter D, is begun with bur holes over the sagittal sinus just behind the coronal suture 6 cm in front of it. The left edge of this opening is just to the left of the sagittal sinus. (b) The placement of retractors through this precoronal bone flap allows exposure of the entire corpus callosum. Once the midline has been determined by identification of the raphe between the two ventricles, removal of the commissure or white matter can proceed rapidly anteriorly and posteriorly. The use of a microdissector passed just posterior to the anterior cerebral arteries allows the genu of the corpus callosum to be completely sectioned. This exposure also allows estimation of a point approximately two-thirds back in anterior corpus callosotomy (stippled area). (c) Detail of a ball-tipped micro nerve hook in the cavum vergae space that keeps the corpus callosum division on midline and prevents straying in either lateral ventricle.

about which pericallosal artery is the right and which is the left, but if there is any variation from normal anatomy, it can be deciphered at this time by following small branches off these arteries either to the right or to the left. It is almost always worthwhile to dissect the two arteries apart so that the actual callosotomy can be made between them. If this is not possible without significant manipulation of the artery, it can also be arranged to do the callosotomy on one side or the other of both of the arteries, but this generally makes it more difficult to stay on the true midline as the artery crosses back and forth over the surgical field.

Once the corpus callosum is well exposed from the genu to the body and the splenium, the desired posterior margin of the callosotomy can be determined through visual inspection and direct measurement and/or image guidance. The corpus callosum is entered in the midline at the level of the coronal suture (► Fig. 74.2). Even in a patient without a cavum septum evident on MR imaging, there is usually a small space between the two medial surfaces of the lateral ventricle and the corpus callosum, and the goal on coming through the corpus callosum is to enter through to this space, leaving the ependyma intact so as not to enter into the ventricle. Avoiding entry into the ventricles and preserving the ependyma significantly decreases complications related to intraventricular hemorrhage (including chemical meningitis and hydrocephalus). The midline is sometimes marked with a small vein, and when present this can be used as an anatomical guide. If there is inadvertent deviation from

midline, the ependyma may come into view; it appears as a translucent layer with dark-appearing underlying ventricular fluid. If deviated from midline, effort should be made to explore slightly to the right and left to find this midline raphe. Once the raphe is located, a small, ball-tipped microdissector can be inserted into it, and this can be used to pull the corpus callosum up from below toward the aspirating sucker, dissecting forward toward the genu first and then posteriorly to the splenium later. It is generally possible to stay out of the ventricle entirely by using this maneuver. However, if the ependyma is breached, a small piece of collagen pad can be placed over the opening to prevent intraventricular passage of blood and debris. The callosotomy is continued anteriorly in the same plane into the genu, following the pathway and orientation of the pericallosal arteries. Once the anterior cerebral arteries are identified on the anterior aspect of the genu, the callosotomy can be safely continued all the way to the anterior communicating artery complex to the level of the anterior commissure, which is visible and deep and posterior to the genu at this point of the dissection.

The decision about the posterior extent of disconnection is planned preoperatively based on the review of the sagittal MRI. The length of disconnection, measured from the anterior tip of the genu, is about two-thirds the length of the total corpus and avoids sectioning of the splenium. Image guidance techniques can be very useful in gauging the distance back on the corpus callosum in anterior callosotomy to avoid inserting modified disposable rulers or patties. The disconnection then proceeds

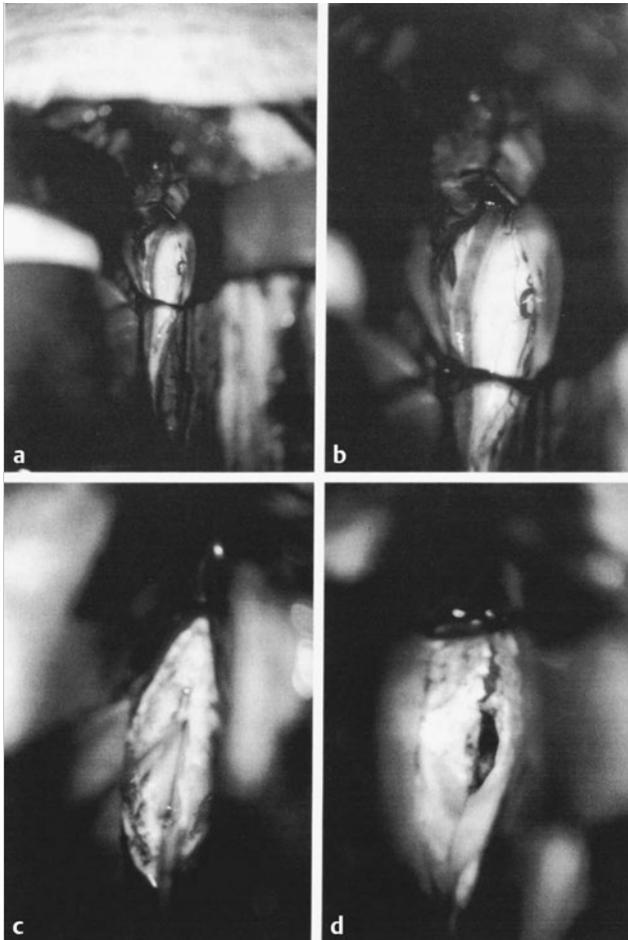


Fig. 74.2 Photographs through the operating microscope show exposure of the corpus callosum and identification of the midline raphe with corpus callosum division, as described. (a) Low-magnification and (b) higher-magnification views of the approach to the corpus callosum, which is distinctly whiter than the abutting cingulate cortex. (c) Aspiration of the callosal white matter shows the midline raphe between the ventricles, at the floor of the cavum vergae. Complete removal of the callosal fibers is ensured by proceeding forward with the ball-tipped micro nerve hook just above the raphe. (d) Further forward, the raphe falls away as the corpus callosum curves around the genu. The passage of a dissector between the superior part of the callosal fibers and the arachnoid allows the genu to be pulled posteriorly and divided, with direct visualization of the arachnoid down to the region of the anterior communicating artery complex.

posteriorly with the same technique used in the anterior division. After adjustment of the patient's position head down with a small amount of Trendelenburg and of the angle of the microscope, the midline cleft between the ventricles is followed posteriorly to maintain a midline position and avoid injury to the corona radiata on either side of the corpus callosum. The cleft usually blurs posteriorly as the ventricles diverge from each other to the atria and then the temporal horns. The midline, though, can still be followed, and the posterior margin of the splenium (in the case of a total callosotomy) can be visualized. The callosotomy is completed through the splenium to the posterior commissure, with the arachnoid surrounding the vein of Galen left intact.

After completion of the callosotomy, hemostasis is meticulously achieved. A piece of collagen pad is cut to the appropriate size and positioned in the callosotomy defect. The dura is then reapproximated, the bone flap replaced, and the wound closed with standard technique.

74.2 Neurostimulation

Electrical stimulation for the treatment of seizures can be applied to various targets within the central and peripheral nervous systems. The goal of neurostimulation is to inhibit epileptogenicity; however, the mechanisms of action are poorly understood. Both open-loop and closed-loop systems are used for neurostimulation. Deep brain stimulation (DBS) and vagus nerve stimulation (VNS) are the two open-loop systems most commonly employed, in which continuous stimulation is applied according to set algorithms without regard to whether the patient is having a seizure or not. In contrast, closed-loop applications, such as regional neurostimulation (RNS), provide acute stimulation only when abnormal electrical activity is detected.^{90–92} The closed-loop algorithms required to detect the ictal state, as well as the electrical stimulation parameters necessary for seizure termination in both open- and closed-loop systems, are areas of active research.^{93–95}

74.2.1 Regional Neurostimulation

Closed-loop systems are dynamic circuits that use real-time feedback to deliver stimulation to a specific areas, either to the area of an epileptic focus or through circuit networks shared by the focus, only in a time of anticipated need. As a self-modulating system, RNS has the potential for tremendous sophistication. In its current state, RNS is of limited utility and can be applied only to definable epileptic foci. Fairly simple algorithms are used for RNS execution. Nonetheless, the techniques used for the detection of ictal activity and the delivery of electrical stimulation are areas of active research, and this is a technology that will certainly continue to evolve.^{93–95} Current evidence suggests that changes in the dynamics of electrical activity can be detected well before the development of seizures,⁹⁰ thus allowing earlier stimulation and potentially more effective treatment.

74.2.2 Deep Brain Stimulation

In contrast to a closed-loop system, an open-loop system like DBS applies continuous stimulation to deep brain nuclei without reference to the brain's electrical activity. A wide variety of targets for the treatment of refractory seizures have been evaluated and include the cerebellum, basal ganglia, subthalamic nucleus, and thalamus (centromedian, anterior thalamic nuclei).^{96–101} Although the results of many of the studies show promise, definitive conclusions are often prohibited by small patient populations and a lack of long-term follow-up. Stimulation of the anterior thalamus, on the other hand, has been thoroughly studied. The randomized controlled SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) trial demonstrated a median rate of seizure reduction of 56% by 2 years and a higher than 50% rate of seizure reduction in 54% of patients with medically refractory partial seizures.¹⁰² During the blinded phase of the study, patients with temporal lobe

seizures showed a greater benefit than with those with extra-temporal or multifocal seizure onsets.

74.2.3 Vagus Nerve Stimulation

The prototypic neurostimulation procedure for epilepsy—and the only antiepileptic stimulation treatment currently approved by the Food and Drug Administration (FDA)—is VNS. VNS was first attempted in a human patient in 1988¹⁰³ and was approved by the FDA in 1997 as an adjunctive treatment for medically refractory partial-onset epilepsy. The rationale for the intermittent unilateral stimulation of the cervical portion of the vagus nerve is based on the long-standing observation in laboratory animals that vagal stimulation produces EEG cortical desynchronization.^{104,105} A growing body of literature demonstrates that VNS is a safe, well-tolerated, and efficacious palliative treatment for both partial-onset and generalized medically refractory epilepsies.

Vagus Nerve Anatomy and Physiology

The vagus nerve (cranial nerve X) is a mixed motor and sensory nerve. Its wandering innervation extends from the medulla to the splenic flexure of the colon. Efferent fibers comprise only 20% the vagus nerve, carrying branchial motor efferents to the larynx and pharynx and parasympathetic visceral efferents to the pharynx, larynx, and organs of the thorax and abdomen.¹⁰⁶ The remaining 80% of the vagus nerve carries primarily visceral afferent fibers from the neck, thorax, and abdomen and from stretch receptors in the aortic arch and chemoreceptors in the carotid bodies; a small proportion of fibers also carry somatic sensory (external auditory meatus, tympanic membrane) and special sensory (taste) afferents. Asymmetric development leads to an association of the right vagus nerve with the cardiac atria and of the left vagus nerve with the cardiac ventricles, with relatively less dense vagal innervation of the ventricles.¹⁰⁷ This asymmetric cardiac innervation is the likely reason why unilateral stimulation of the left vagus nerve minimizes cardiovascular side effects in humans.

Vagus nerve fibers distribute widely through the central nervous system, both monosynaptically and through the nucleus of the solitary tract (NTS).¹⁰⁸ Although a small number of fibers connect directly to the spinal trigeminal nucleus and the reticular formation, the vast majority of vagal afferents are carried to the NTS via sensory neurons of the nodose ganglion. Three major output pathways distribute afferent vagal information from the NTS to dispersed central nervous system structures.^{109,110} The first pathway mediates feedback control of the heart rate (baroreceptor reflex) and respiration (Hering-Breuer reflex) via autonomic preganglionic and somatic motor neurons in the medulla and spinal cord, while the second pathway targets the reticular formation of the medulla and controls autonomic and respiratory reflexes.^{111,112} The third major NTS output pathway projects to forebrain structures via the parabrachial nucleus of the dorsal pons and is the most likely mediator of VNS anticonvulsant activity. The parabrachial nucleus has widespread projections to the insular, infralimbic, and lateral frontal cortex, as well as to the thalamus, hypothalamus, amygdala, and basal forebrain.¹¹³ Via the amygdala, output pathways from the NTS project to other limbic structures

including the hippocampus and entorhinal cortex. Notably, there is direct parabrachial input to the intralaminar and midline nuclei of the thalamus, which project widely throughout the cerebral cortex and may influence both physiologic and pathologic cortical synchronization.^{114,115}

Most cerebral structures are three or more synapses away from the vagus nerve; this relatively large distance between the brainstem vagal afferent system and the different cortical sites of epileptogenesis responsive to VNS suggests a role for systems projecting diffusely between the brainstem and forebrain. Various anatomical pathways are activated during VNS, but the specific circuitry responsible for anticonvulsant activity and the nature of the neurophysiologic changes (e.g., increased vs. decreased activity) remain unknown. Examination of *fos* gene product expression following brief intermittent VNS in rodents showed elevated neuronal activity in the amygdala and limbic neocortex (cingulate and retrosplenial cortex), both of which are implicated in epileptogenesis, as well as in hypothalamic and noradrenergic nuclei.¹¹⁶ Positron emission tomography (PET) neuroimaging studies have shown acute increases in regional cerebral blood flow to the medulla, right postcentral gyrus, and bilateral thalamus, hypothalamus, and insular cortex during VNS, with deactivation bilaterally in the hippocampus, amygdala, and posterior cingulate gyrus.¹¹⁷ A higher level of stimulation affected the same structures as the low-level stimulation, but with increased volumes of activation and deactivation, and additionally activated the bilateral orbitofrontal gyrus, right entorhinal cortex, and right temporal pole. In follow-up PET studies, only left and right thalamic activation was correlated with decreased seizure frequency after 3 months of VNS.¹¹⁸ More recently, functional MR imaging (fMRI) during VNS demonstrated robust activation of the thalamus and insular cortex, with post-VNS seizure reduction also associated with thalamic activation.^{119,120}

Vagus Nerve Stimulation: Mechanism of Seizure Prevention

The diffuse cortical effects of VNS can be observed on the EEG, as in the early studies, which showed cortical desynchronization in cats after cervical VNS.^{104,105} Animal studies further demonstrated that repetitive vagal stimulation can induce either synchronization or desynchronization of the EEG, depending on stimulation frequency and current strength.^{105,121,122} Specifically, high-frequency NTS stimulation (>30 Hz) induces EEG desynchronization, whereas slower stimulation (<17 Hz) induces synchronization.¹²³ This preferential induction of synchronization with lower-intensity and slower-frequency stimulation and desynchronization with higher-intensity and faster-frequency stimulation may result from the differential recruitment of vagal afferent fibers, with desynchronization requiring activation of smaller-diameter unmyelinated fibers. In contrast, VNS in humans does not generally produce obvious or readily observable synchronization or desynchronization of the EEG.^{124,125} VNS produces evoked potentials of cerebral origin in scalp EEG only at stimulation intensities higher than those used clinically,^{126,127} but there is evidence that chronic VNS results in altered somatosensory and visual evoked potentials, which presumably reflect long-term changes in underlying neural circuitry.^{128,129}

In addition to its effect on the underlying physiologic EEG, VNS has observable effects on pathologic interictal epileptiform

discharges and seizure-like activity. The frequency of penicillin-induced focal interictal spikes in a rodent model of acute epilepsy is reduced 33% during VNS, an effect that can persist for minutes after the termination of electrical stimulation.¹³⁰ VNS has similar abortive effects on acute chemically induced seizures in rodent and canine models, an effect dependent on the activation of unmyelinated vagal C fibers.^{130–132} Although VNS in humans produces no observable changes in the interictal scalp EEG,¹²⁴ interictal epileptiform sharp waves recorded with hippocampal depth electrodes were decreased by 30-Hz vagal stimulation and increased by 5-Hz stimulation in a case report.¹³³ VNS also has acute prophylactic anticonvulsant effects that extend beyond the duration of stimulation, decreasing the number and duration of pentylenetetrazol-induced seizures in rats for up to 10 minutes after the termination of stimulation.¹³⁴ Furthermore, the prophylactic anticonvulsant effect of chronic VNS is progressive; chronic vagal stimulation over weeks is accompanied by decreasing seizure activity in an alumina gel primate model,¹³⁵ and longer-term VNS (up to 12 months) in human patients induces initial clustering of EEG epileptiform activity followed by progressively increased spike-free intervals.¹³⁶

Despite accumulating data, the precise mechanism underlying VNS-mediated anticonvulsant activity remains poorly understood. Antiepileptic drugs exert their effect through the modulation of voltage-dependent sodium and calcium currents and γ -aminobutyric acid (GABA)-mediated inhibition.^{137,138} Whereas antiepileptic drugs function by directly modulating cellular signaling on a molecular level, VNS functions through the stimulation of widely projecting brainstem pathways, which may result in the activation or inhibition of target regions. Thalamic nuclei are likely involved, given their consistent activation in PET and fMRI studies, the correlation between thalamic activation and seizure reduction, the diffuse nature of thalamocortical projections, and their role in physiologic and pathologic cortical synchronization.^{67,115,139} Noradrenergic activity also may be central to VNS function; noradrenergic nuclei show increase *fos* expression following VNS,¹¹⁶ and chemical lesion of the locus ceruleus significantly attenuates VNS-induced seizure suppression in rats.¹⁴⁰ In VNS-implanted rats, it has been demonstrated that stimulation increases norepinephrine concentration in the prefrontal cortex.¹⁴¹ Other associated biochemical changes include increased expression of brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) in the hippocampus and cerebral cortex, and decreased expression of nerve growth factor in the hippocampus. It has also been postulated that VNS affects seizure thresholds by modulating inhibitory neurotransmission; chronic VNS is associated with increased cerebrospinal fluid levels of the inhibitory neurotransmitter GABA, but these changes were not correlated to the degree of seizure reduction.¹⁴²

Vagus Nerve Stimulation: Outcomes

VNS has been shown to be effective in managing both partial and generalized seizures, with the primary indicator of efficacy being a reduction of seizure frequency.^{143–145} In the multicenter randomized double-blinded controlled EO3 and EO5 studies, patients with medically refractory partial-onset seizures were implanted with a VNS system and received either a high-stimulation (30 Hz, 30 seconds on, 5 minutes off, 500- μ s pulse width)

or a low-stimulation (1 Hz, 30 seconds on, 90 to 180 minutes off, 130- μ s pulse width) protocol for 12 weeks. Patients receiving the higher-stimulation treatment experienced mean reductions in seizure frequency of 24.5% and 28% in the two studies, compared with 6.1% and 15% in patients receiving the lower-stimulation protocol, but both the high- and the low-stimulation treatment produced statistically and clinically significant seizure decrement. In a nonrandomized treatment trial of 24 patients, VNS also reduced the frequency of generalized seizures by 46% after 3 months of stimulation.¹⁴⁴

Although the current FDA indication for VNS covers patients 12 years and older, clinical data suggest that VNS has efficacy in younger pediatric patients as well. A study of 60 patients age 3 to 18 years (median age, 15 years; 16 patients younger than 12 years) demonstrated a 23% median decrease in seizure frequency after 3 months of stimulation, with a progressive benefit of continuing stimulation (31%, 34%, and 42% at 6, 12, and 18 months, respectively); patients had either partial or generalized tonic-clonic seizures (27%), and the response rate was not specific to seizure type.¹⁴⁶ Likewise, an uncontrolled retrospective study of patients between 11 months and 16 years of age with complex partial or generalized (atonic, absence, tonic-clonic) seizures reported improvements in seizure reduction regardless of age and seizure type.¹⁴⁷ VNS has also been used successfully to manage patients with Lennox-Gastaut syndrome. In 13 patients with Lennox-Gastaut syndrome (4 to 44 years of age), 6 months of VNS produced a 52% median reduction in seizure frequency, including 3 patients with a decrease of more than 90%.¹⁴⁸ In a smaller study of pediatric patients with epileptic encephalopathies, there was a greater than 50% reduction of seizure frequency in 4 (27%) of 15 patients, and a significant improvement in perceived treatment side effects and general behavior was noted, although no significant group improvement in seizure frequency or severity, adaptive behavior, or EEG.¹⁴⁹ In a recent randomized controlled study of 41 children with intractable epilepsy (35 with localization-related epilepsy and 6 with generalized epilepsy), VNS reduced seizure frequency by 50% or more in 26% of participants.¹⁵⁰

In general, VNS has proved to be safe and well tolerated.^{151–153} The most commonly reported side effects include dysphonia (20%) and cough (6%), which most often occur during the stimulation phases and resolve during the quiescent phase of the stimulatory algorithm.⁸ In the randomized double-blinded EO3 and EO5 studies, only voice alteration was more frequent in the high-stimulation than in the low-stimulation population; less common adverse effects included throat pain, nonspecific pain, dyspnea, paresthesias, dyspepsia, vomiting, and infection, with adverse effects in these two studies rated mild or moderate 99% of the time and with no observed negative impact on cognition, affect, or coordination.^{143,145} The impact of VNS on mood and cognition was looked at more closely in a recent randomized clinical trial.¹⁵⁴ Consistent with studies supporting a role of VNS for treatment-resistant depression, the authors found that VNS not only did not negatively impact mood or behavior but also led to a generalized improvement in mood for the entire group. The observed benefit was unrelated to the effect on seizure frequency. Furthermore, there is a low rate of surgical complications, with device failure (2.7%) and deep infection (3.5%) the most commonly observed in a retrospective study of pediatric patients undergoing device implantation.¹⁵⁵ One of the authors (P.D.A.) has had less than a 2%

incidence of infection and only a 0.4% incidence of deep infection requiring removal of the device. Erosion of the pulse generator through the chest wall can be a concern in children or debilitated patients with little subcutaneous fat but is a relatively rare occurrence that can be avoided with a subpectoral implantation. Furthermore, the next generations of devices are thinner and smaller, making this even less of an issue.

Cardiovascular adverse effects are a theoretical concern given the cardiac efferents from the vagus nerve, but significant cardiac complications have not been observed with VNS. A small number of cases have been reported of transient bradycardia or ventricular asystole during intraoperative testing of the device leads (estimated occurrence rate of 0.1%); proper caution dictates the use of test stimulation before generator implantation and close cardiac monitoring during the procedure.^{156,157} Despite the variable effects on cardiac rhythm observed during stimulation,¹⁵⁸ studies reveal no long-term cardiovascular effects involving arrhythmia or heart failure.

Vagus Nerve Stimulation: Presurgical Counseling

During the preoperative visit, we have found it useful to address expectations and counsel families that the therapeutic response to VNS is difficult to predict. The median response is an approximately 50% reduction in seizures, but a wide spectrum has been reported, and responses can be better or worse. In terms of patient selection, it is critical that the neurosurgeon first ensure that the patient does not qualify for more definitive, potentially curable procedures, such as focal resection, because VNS is merely a palliative therapy. It is also important that certain diagnostic studies, such as high-field-strength MR imaging, which requires the body magnet to send or receive signal, and magnetoencephalography, may not be possible in many centers after the VNS device is inserted. If these tests are important as part of the continued work-up or ongoing evaluation, steps to schedule them before the actual implantation should perhaps be considered. Other parts of the diagnostic work-up, such as routine head coil MR imaging and EEG, and even invasive monitoring, can be done with the VNS device in place and functioning if necessary.

Vagus Nerve Stimulation: Surgical Technique

Although several variations have been developed for placement of the VNS device, virtually the only absolutely necessary steps are to ensure that the electrode leads contact the correct nerve in the correct vertical orientation, and that the post-generator device be accessible to the patient for magnet activation and to the physician for reprogramming.

In the initial descriptions of the procedures,^{116,117} a vertical incision over the carotid sheath was described, and a horizontal incision more than 4 cm below the clavicle for placement of the device was suggested. Improvements to increase comfort and cosmetic appearance after ultimate placement of the VNS device have been developed subsequently over the years. Examples include the use of a single longer incision both to access the nerve and to make a pocket for the device on the chest or lateral pectoral incision.¹¹⁸

We have found that the most satisfactory approach in children is begun by making both incisions in the direction of skin

creases, which tends to minimize the amount of widening of the incision and gives a better overall cosmetic result (► Fig. 74.3). It also becomes possible to use incisions that are quite limited (as little as 2 cm in the neck and 2.5 cm in the axillary region), and to place the device under the pectoralis muscle rather than over the pectoralis muscle, particularly in very young or very thin patients. Most patients have adequate subcutaneous tissue to hide and cushion the device, especially with the newer small generators (Model 103 and beyond). Because the generation of a subcutaneous pocket is relatively trivial and the creation of a subpectoral pocket is more common in pediatric than in adult practice, this description focuses on subpectoral placement.

For the optimal placement of the device deep to the pectoralis muscle, it is important that the incision that gives access to this region be lateral and inferior to the margin of the pectoralis itself. For this, surgical scrub preparation of the axillary region and the rectangle extending up to include the anterior neck must be done. Typically, for the placement of a new device, we elevate the left side of the chest, abduct the shoulder slightly, and keep the left arm flexed somewhat, so that the arm falls out of the way of the access to the subpectoral region. The neck is positioned in slight extension and turned slightly to the right to expose the left side, but not so much as to bring the sternocleidomastoid muscle sharply across the carotid sheath. The optimal location for the carotid sheath dissection can be estimated by palpating the carotid artery and finding the point where the pulse burst becomes clear over the edge of the sternocleidomastoid. It is important to realize that the most desirable place for electrode placement is in the lower third of the neck, well below the carotid bifurcation, the area with which neurosurgeons have the greatest anatomical familiarity.

We initiate the procedure first with the incision for the generator pocket. There are different options of several different types of incisions, either on the chest wall itself for subcutaneous placement or more laterally, especially if the plan is to place the generator subpectorally. An incision parallel to the edge of the pectoralis muscle will often result in a widened scar, so we use one that follows the crease lines of the skin and therefore is almost perpendicular to this muscle approximately 5 cm below the level of the clavicle. This gives far better healing and a better cosmetic result.

Depending on the amount of subcutaneous adipose tissue, the surgeon opens the incision and then bluntly works to the edge of the pectoralis major. A small hollow is opened sharply and then, once opened, dissected bluntly to make a space large enough, either between the pectoralis major and minor or deep to the pectoralis minor, to easily hold the pulse generator. In smaller patients, this may be difficult and results in the generator being too laterally placed; therefore, subcutaneous placement is required instead. In this regard, the major advantage of thinner and smaller pulse generators, including the current Model 103, is that the incision does not have to be as long to admit and then secure the device. Once the plane is generated, an antibiotic- and/or a Betadine-soaked large sponge can be placed in the cavity as the surgeon proceeds to the cervical incision.

The neck incision, which may be as small as 2 to 2.5 cm, is made in the skin, again parallel to and often in a skin crease. The dissection is carried down to the platysma, where the planes are elevated to provide greater exposure. The platysma can be split parallel to the fibers, perpendicular to the skin

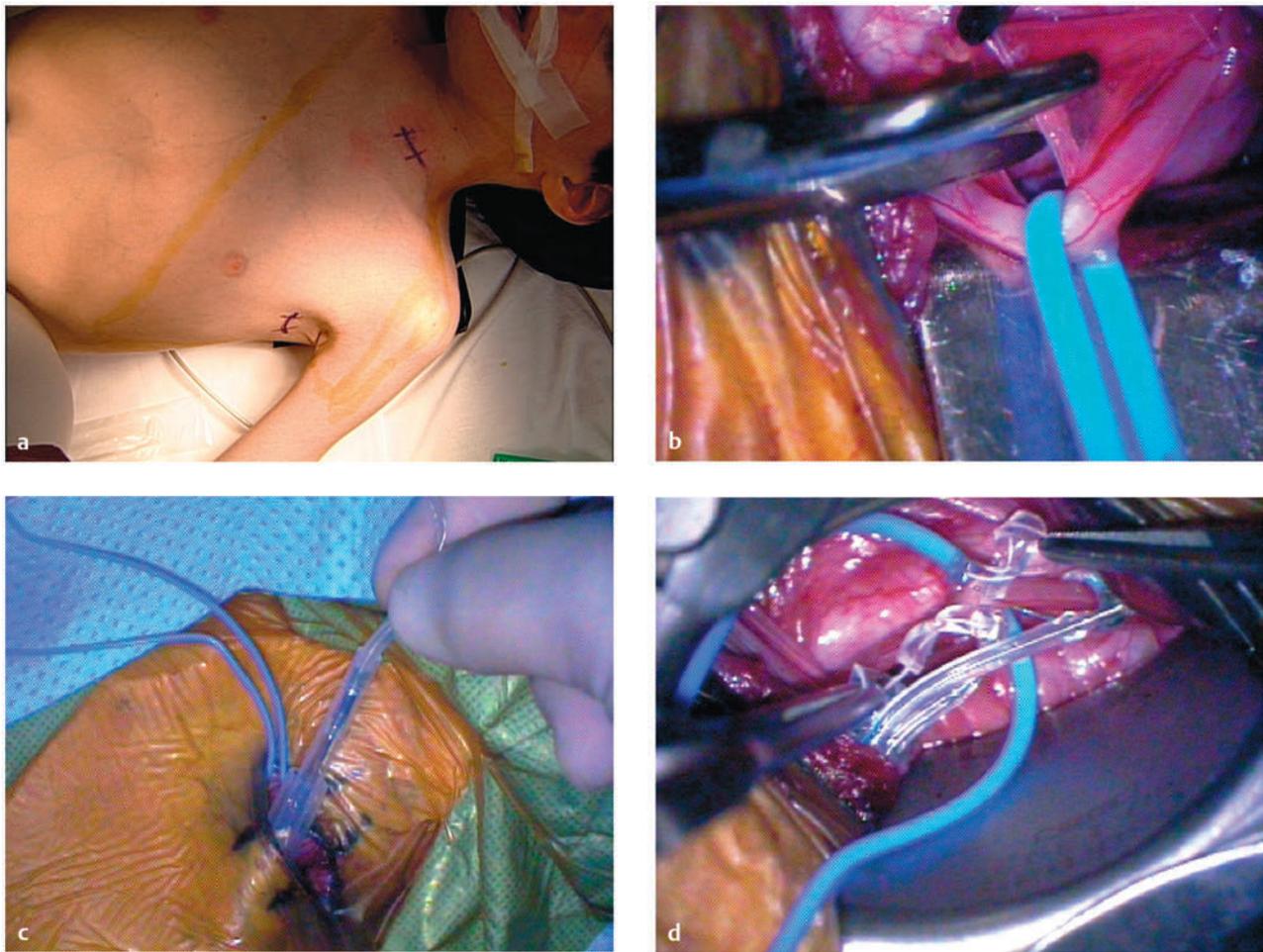


Fig. 74.3 Steps in the placement of a vagus nerve stimulator. (a) With the patient supine, incisions are marked in the direction of Langer lines in the skin, arranged to allow access to the carotid sheath in the lower neck, and tunneled up from the axillary pocket to the neck incision. This positioning allows an approach to the neck from both sides of the operating table and an approach to the axilla from the patient's left. (b) Short Cloward retractors provide visualization while the vagus nerve is dissected free from the carotid sheath. (c) The tunneling tool contains two concentric plastic tubes, the inner of which snugly fits the single-pin connector of the Model 303 or 304 leads. (d) The helices are placed around the nerve. (*continued*)

incision along the anterior border of the sternocleidomastoid, and more vertically to increase the exposure. Dissection can usually be followed down in a blunt way toward the palpable carotid pulse in an avascular plane, in a technique similar to what one would use for a carotid endarterectomy.

The omohyoid and other strap muscles are retracted inferiorly and medially as the sternocleidomastoid is retracted laterally with self-retaining retractors to provide the requisite exposure. It is possible to find the carotid sheath very efficiently and start to identify the translucent fascial plane that invests the jugular vein and internal carotid artery.

Usually, with gentle retraction and dissection in line with the vessels between the jugular and the carotid, the vagus nerve can be visualized, most often just posterior and lateral to the carotid. It is a large-diameter nerve and is usually more adherent to the jugular vein than to the carotid artery. Sharp dissection of the carotid sheath on both sides of the vagus nerve mobilizes it sufficiently so that a vessel loop can be passed underneath and around it. Early loop placement facilitates

visualization of the planes and mobilization without injury to the nerve. In general, approximately 2.5 to 3 cm of the nerve should be dissected free of the adherent sheath to provide enough length for the electrode leads. The topology of the investing sheath is such that two parallel incisions are made, one on either side of the nerve.

The choice of 2- or 3-mm helices for the electrodes depends on the caliber of the nerve. The packaging is opened once the nerve is visualized to decrease the time of exposure of the components. The electrodes are tunneled with the manufacturer-supplied tunneling device, which includes an inner and an outer tunneling tube, from the axillary incision medial and superior in the pocket toward the neck incision. A bend can be made in the device to make the necessary turn, or because of the very short distance involved, the tunneler can be used without bending the leading segment. Once tunneling has proceeded over the edge of the clavicle and into the superior surgical cavity deep to the platysma, the pointed tip of the probe is removed, and the electrode connectors are inserted into the



Fig. 74.3 (continued) (e) Silastic (Dow Corning, Midland, MI) anchors are sutured to the carotid sheath tissue to create the lower strain-relief loop in the cable. With a small incision, all three helices may not be seen in one view. Here, the anchor helix (with no electrical contact) is shown at the left, and the negative lead is shown in the cranial direction from it. The helix in the most cranial position, the positive lead, encircles the vagus nerve, unseen to the right. After the generator is secured with the torque wrench (f) and placed in its pocket (g), impedance testing with the handheld programmer is performed (h). Incisions are closed with subcuticular absorbable suture and epidermal adhesive.

inner tubing and pulled from the neck incision down into the pocket incision. We often place an antibiotic-soaked cover to reduce exposure while the leads are placed around the vagus nerve.

The following process of actually putting the helices onto the nerve is simplest to perform and teach in our hands. There are three coils—the negative and positive leads and the anchor or strain reliever. Typically, with very gentle retraction applied to the nerve upward with the vessel loop, and starting at either end and working vertically, each of the electrodes is grasped gently, one at a time for each pair of stringlike attachments in the helices, and stretched slightly to allow opening of the cleft between the helical turns. The superior turn is crossed over from medial to lateral and the inferior is crossed over from lateral to medial to ensure contact of the metal electrode portion of the helix to the nerve. This can be done with one movement of two pairs of forceps to resolve in a revolution and a half of helix around the nerve. The additional part of the helix can be teased into place with a variety of instruments, until the entire helix is entirely wound around the nerve. As a caution, if it seems to be very difficult to get the helix around the nerve, the

problem may be that the surgeon has forgotten that this is truly a right-handed helix system and has tried to put it on in the wrong orientation, which will very likely result in failure.

After the electrodes have been positioned on the nerve, it is necessary to make redundant loops so that movements of the neck do not dislodge the electrodes or put strain on the vagus nerve itself. A small space can be bluntly dissected with a right-angle dissector along the nerve in the carotid sheath going inferiorly and superiorly for these loops. Using the Silastic pledgets included with the electrodes, the doubled part of the cable is passed first inferiorly for a couple of centimeters and secured medially with, preferably and if possible, two tie-downs and 4-0 nonresorbable suture through the middle of the folded wings of the Silastic tie-downs. The loop is then passed superiorly and down parallel to the sternocleidomastoid muscle, where another two Silastic pledgets can be secured to the inner surface of the muscle so that the tie-downs are not easily palpable through the skin. The purpose of these relaxing loops is that movements of the neck, which can cause very dramatic changes in the distance between the sternocleidomastoid muscle and the carotid sheath, result in stretching and pulling on only the part of the cable

between the two tie-downs, and not on the part that is not directly sutured to or otherwise fixed to the nerve.

Vagus Nerve Stimulation: Initial Programming of the Generator Device

Our preference has been to have the devices turned on at the time they are being implanted. Although the risk for cardiac arrhythmias with the initiation of VNS is very low, we prefer to screen with continuous cardiac monitoring for untoward cardiac responses in the controlled environment of the operating room and a monitored bed immediately post operatively. Many practitioners nevertheless do follow the manufacturer's recommendation not to have the device activated at the time of the initial surgery. The pulse generator can be programmed before implantation while it is still in its package. Programming is performed with a handheld mobile device attached to a wand that communicates with the pulse generator via radio-frequency waves.

During the closure, the wand is draped in a sterile fashion, and the device is interrogated again and a lead test performed. The lead test now delivers a current in the range at 0.25 mA (compared with 1 mA in the older software versions), so the risk for cardiac or other autonomic complications during the lead test is less than in earlier models. As discussed below, a severe bradycardia that may need to be treated with vagolytic agents develops in approximately 1 in 600 patients (in the registry including all ages), but these data were reflective of the higher lead test currents.

Vagus Nerve Stimulation: Insertion of the Pulse Generator

The leads themselves are attached and anchored with a single set screw for the single two-contact pin for the Model 103 generator or with two separate electrodes that have separate pins for the Model 104 (which is a modification of the Model 103 designed to accept the older electrode pins). The device is secured in the subcutaneous pocket with nonresorbable suture. When a subcutaneous placement is made for a patient with a thicker adipose layer, the attachment is to the pectoralis major; otherwise, muscle deep to the pocket is used. The muscle is then closed over the pocket with interrupted resorbable sutures. The neck wound is also closed in a multilayered fashion. Care is taken to reapproximate the platysma with braided resorbable suture to ensure a good cosmetic result. The skin is typically closed with resorbable monofilament (4-0 or 5-0) and a subcuticular stitch, with a tissue adhesive placed over the suture line to protect the incisions. Sterile bandages can be placed over the wounds for further protection.

Vagus Nerve Stimulation: Postoperative Care

Patients are advised to keep the incisions clean and dry for several days to a week, and then the outer dressings can be removed. Frequently, these procedures are performed on an outpatient basis, and only the initial perioperative antibiotic dose is given. Interscapular placement of a VNS pulse generator can be used for very young children to prevent wound tampering, but we have found satisfactory results with the more standard subpectoral placement.

Postoperatively, patients are scheduled to visit their physician regularly every few days to weeks. The device is programmed to ramp up the current and to optimize the settings, which most often settle at around 1 mA. In most practices, this is done by a neurologist or epileptologist, although some pediatricians can be instructed through the primary neurologist if the child lives in a rural community or far away from the epilepsy center. The interval between stimulation sessions, the so-called off-time, can be decreased if the patient seems to need more stimulation to achieve a therapeutic effect.

For reasons that are not clear, sometimes even at the same dose of current, the effectiveness of stimulation may increase with time. In some ways, this is the reverse of the phenomenon of kindling, in which a low level of stimulation may eventually cause a seizure; here, long-term low-level repetitive stimulation seems to inhibit seizures. The actual underlying pathophysiology of this is not understood.

74.3 Future Directions

As with most fields in neurosurgery, surgical treatment options for medically refractory epilepsy are trending toward less destructive, more minimally invasive techniques. There has been a paradigm shift of moving away from simply anatomical removal or disconnection procedures to more dynamic systems of neurostimulation. Neurostimulation has several advantages over ablative-type surgeries, including reversibility, a lower risk for permanent neurologic deficits, and the ability to impact multiple foci with a single target. Furthermore, neurostimulation offers the ability to modulate circuits postoperatively, to individualize treatment and to maximize therapeutic benefit. Disadvantages are the need for implantation, potential failure of the technology at the lead or generator level, and the lack of a "cure" for the epilepsy. As a technique, neurostimulation remains in its infancy and is far from realizing its full potential. Most of the current applications involve open-loop systems that provide continuous, round-the-clock stimulation. However, a large research effort is aimed at developing efficacious closed-loop systems to allow the continuous monitoring of brain activity and the delivery of electrical stimulation only when peri-ictal electrical activity is detected. Although closed loop systems are promising, more sophisticated technology is needed for more sensitive and specific detection of abnormal activity.

As the technology continues to advance, the number of potential neural targets for neurostimulation continues to expand. Beyond the multitude of central nervous system targets that have been investigated (as described above), new peripheral targets have emerged. Stimulation of both the trigeminal nerve and glossopharyngeal nerve (branch known as the Hering nerve) has demonstrated potential benefit for the treatment of epilepsy.¹⁵⁹⁻¹⁶² Further bench-top and clinical experimentation is needed to validate its utility.

Farther along the minimally invasive spectrum, repetitive transcranial magnetic stimulation (rTMS) has been introduced as a potential treatment option for epilepsy.¹⁶³ rTMS is a noninvasive technique that uses an extracranial electromagnetic field to induce cortical neuronal currents. The impact of various frequencies and pulse trains on neural excitability has been studied extensively. There is now evidence from several clinical trials that rTMS may be effective in the treatment of seizures.¹⁶⁴⁻¹⁶⁷

Because the electromagnetic force is strongest at the cortical surface, rTMS may be most effective in the treatment of cortical epileptogenic foci. Currently, investigators are working to optimize stimulation parameters and to characterize the efficacy of rTMS for various seizure disorders.

A separate frontier focuses on cellular and molecular strategies for seizure reduction in medically refractory epilepsy. Many avenues are currently being explored, including the application of stem cell–based therapies, gene therapy (e.g., galanin, neuropeptide Y, neurotrophic factors, adenosine-based therapies), focal drug delivery (e.g., delivery directly to a seizure focus, cerebrospinal fluid–disseminated delivery), and optogenetics.^{162,168} Although most of these strategies remain at the basic science level of investigation, they all demonstrate clinical promise, and collaboration with neurosurgeons will be required for implantation and other surgically based modes of delivery.

Pearls

- Any child with refractory epilepsy who is not a good candidate for a resective procedure (i.e., nonlocalizable partial complex epilepsy, generalized seizures, multifocal epilepsy) should be considered for nonresective approaches, such as disconnection procedures or neurostimulation. Discussion should begin with the families early so that they understand that failure of medicines will lead to a recommendation for surgical intervention.
- Corpus callosotomy is a disconnection procedure that is highly effective for drop attacks and atonic seizures.
- One-stage, complete corpus callosotomy may be indicated for patients with severe neurologic deficits or neurocognitive/speech impairment.
- Anterior two-thirds callosotomy may be appropriate for patients who can read or are expected to be able to read in the future.
- Callosotomy can be performed through a small craniotomy just in front of the bregma, but a slightly larger craniotomy enables the surgeon to avoid bridging veins by changing the angle of the approach.
- Finding the exact midline within the corpus callosum allows dissection of the raphe between the ventricles and in most cases permits callosotomy without entry into the ventricular system.
- Neurostimulation can be divided into closed- and open-loop systems.
- Open-loop systems, such as DBS and VNS, provide continuous neurostimulation.
- Closed-loop systems, such as RNS, monitor for ictal activity and provide neurostimulation only when prompted.
- Despite FDA labeling for use in patients with refractory partial epilepsy who are 12 years old or older, in our experience, the results for children younger than age 12 are as good if not better than those for older patients. Because of the low risk of surgical implantation and the high risk of inadequately treated intractable seizures, a recommendation for surgical evaluation and ultimately VNS as indicated should be introduced to the family early in the discussion of options.
- Placement of the vagus nerve generator deep to the pectoralis may be appropriate in very young or very thin children.

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75 Hemispherectomy

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Intractable epilepsy is a devastating disease, not only for the patient and family but also for the primary healthcare provider, neurologist, and treating neurosurgeon. Neurosurgical options include invasive monitoring with tailored resection, multilobar removal, multiple subpial transections, and hemispherectomy involving a variety of techniques. This chapter provides an overview of hemispherectomy—its history, the neurosurgical options and indications, techniques, and outcome.

75.1 History

75.1.1 Anatomical Hemispherectomy

The removal of one cerebral hemisphere, or hemispherectomy, was initially described for the control and potential cure of malignant glioma. In 1928, Dandy described a series of five patients in whom an anatomical hemispherectomy was performed by ligating the main cerebral arteries, dissecting the hemisphere off the falx medially, and incising along the corpus callosum and internal capsule, thus delivering the hemisphere.¹ Gardner also published his results on hemispherectomy for gliomas in 1933.² Although the mortality of the procedure was high, on the order of 40 to 66%, both surgeons felt that the risk could be countered by an extended life span.^{1,2} Sadly, improved survival was never fully realized, and patients lived out the remainder of their lives with the added functional impairments created by the surgery.

McKenzie was the first to perform a hemispherectomy for epilepsy in 1938. The patient was a woman who had intractable epilepsy associated with infantile hemiplegia. Krynauw presented a series of 12 patients with infantile hemiplegia and popularized the technique in 1950.^{3–5} Krynauw reported that the main indication for surgery was not preoperative hemiplegia; rather, it was persistence of seizures and resultant cognitive impairment. In his experience, focal surgery might occasionally stop the seizures, but there would be no improvement in mental functioning or physical disability. Krynauw believed that any residual diseased hemisphere would continue to emit electrical discharges that would eventually spread to and involve the anatomically normal hemisphere, thereby potentially continuing to affect intellect as well as inducing secondary foci of epileptogenesis. Thus, he advocated removal of the entire hemisphere.⁵

The initial enthusiasm for hemispherectomy waned when in 1966 Oppenheimer and Griffith reported 3 delayed deaths in a series of 17 patients with anatomical hemispherectomy. Autopsies revealed obstructive hydrocephalus with superficial hemosiderosis, which was thought to be due to repeated episodes of bleeding within the cranial cavity. They suggested that to decrease the risk for hemosiderosis, the abnormal hemisphere should be functionally disconnected and left in place with an intact ventricular lining or that, as an alternative, the ipsilateral ventricular cavity should be occluded from contact with the other side.⁶

Modifications and variations of the neurosurgical technique ensued. Wilson initially discussed decreasing the volume of the

hemispheric cavity in 1968, and Adams further illustrated this concept in 1983 with his “Oxford” modification, which consisted of two steps: First, the ipsilateral foramen of Monro was plugged with muscle to prevent the drainage of blood products into the ventricles; second, the dura was stripped off the bone and tacked to the falx, the tentorium, and the floor of anterior and middle cranial fossae to reduce the volume of the cavity and thus expand the extradural space.^{7–9} The Peacock modification included drainage of the hemispherectomy cavity with a subdural peritoneal shunt.¹⁰ Anatomical hemispherectomy achieves good seizure control, with 80 to 90% of patients obtaining an Engel Class I or II outcome.^{11,12}

75.1.2 Functional Hemispherectomy

In 1974, Rasmussen developed the functional hemispherectomy. This was after subtotal hemispherectomies had been performed in a series of 48 patients from 1937 to 1971 to decrease the risk for hemosiderosis yet resulted in worsened seizure control.⁹ Rasmussen’s procedure involved a subtotal anatomical hemispherectomy with disconnection of the remaining cerebrum from the contralateral hemisphere to obtain the same overall result as that of an anatomical hemispherectomy.^{9,13} The remaining tissue protected the brain from hemosiderosis, but the result was similar to that of an anatomical hemispherectomy, with a seizure-free rate of 75%.³ As well, the incidence of postoperative hydrocephalus was less because a greater amount of the subarachnoid space was left intact.¹³

75.1.3 Hemispherotomy

Other modifications to Rasmussen’s first description of functional hemispherotomy have been made. The techniques differ from one another in regard to the volume of resected brain; the route of access to the lateral ventricle; whether insular resection, hippocampal resection, or disconnection is performed; and whether there is vascular preservation or sacrifice in the peri-insular area.³ The term *hemispherotomy* describes a small amount of cerebral resection with extensive disconnection. In the 1990s, Delalande and colleagues described a vertical approach, while Ville-mure et al and Schramm et al described a lateral approach.^{3,8,14,15} Seizure freedom rates ranged from 74 to 85%.^{3,16} Details are further elucidated in the section on surgical technique.

75.1.4 Hemidecortication

In the initial description, hemidecortication or hemicortication was similar to hemispherectomy; however, instead of removal of the hemisphere en bloc, a small amount of white matter was left over the ventricular system.¹⁷ Winston in 1992 and Hoffman in 1993 further detailed the procedure as “degloving” of the cerebrum because the cortical gray matter was resected down to the white matter, with preservation of the underlying white matter and ventricular system.^{3,12,18} This prevented bloody contamination of the ventricular system. The main problem with this procedure is blood loss and the technical

difficulty of performing complete cortical resections on the medial and basal sides of the lobes.^{3,19,20} However, hemidecortication has resulted in long-term seizure freedom in 50 to 80% of patients, depending on their underlying disorder. If the anatomy of a hemispherectomy is unfavorable to ventricular approaches, then hemidecortication should be considered for patients with severe seizure disorders.²⁰

75.2 Neurosurgical Procedure

75.2.1 Indications for Surgery

To identify a surgical candidate, the concept of medically intractable seizures is raised. Interestingly, what defines medically intractable seizures is not always agreed upon in the literature. Intractability is defined as failure of three first-line antiepileptic medications in infants, whereas in adults, a failure of two antiepileptic medications over 2 years has been used to define intractability. However, in infants with frequent seizures, the duration of drug trials may be brief, and there is a risk with waiting because irreversible cognitive deficits may develop. As well, an early age at seizure onset, a remote symptomatic etiology, infantile spasms, status epilepticus, a poor response to short-term antiepileptic therapy, and failure of an initial antiepileptic drug trial can all predict intractability.²¹ Other indications for surgery include a seizure disorder limited to one hemisphere for which multifocal resections would seem inadequate.²² Preoperative hemiparesis or hemiplegia is preferable because it lessens the postoperative deficit; however, it is not mandatory because there are certain progressive conditions with a well-known natural history that result in the worsening of motor and cognitive function. Catastrophic infantile epilepsy syndromes causing multiple daily seizures put the brain at developmental risk. Therefore, these children may be considered candidates for early surgery because hemispherectomy may avert a decline in cognitive function.³ Diffuse hemispheric disorders for which hemispherectomy has been employed include Sturge-Weber syndrome, cortical dysplasia, hemimegalencephaly, Rasmussen syndrome, porencephalic cyst, and hemiconvulsion-hemiplegia-epilepsy syndrome.^{3,22} (► Fig. 75.1 and ► Fig. 75.2)

Sturge-Weber Syndrome

Patients with Sturge-Weber syndrome typically have hypertrophic pial vessels, and the venous sinuses and veins are frequently absent. The result is a strong retrograde venous flow into the ventricles, and the aberrant cerebral vasculature creates a hypoxic environment as blood is shunted away from the parenchyma. This leads to cellular damage and secondary seizures. Patients typically present with seizures in the first year of life, which begin as simple or complex partial seizures that can secondarily generalize. In patients with diffuse Sturge-Weber syndrome, hemispherectomy is recommended early because their condition will progress to intractable epilepsy, hemiplegia, and cognitive impairment.^{3,22}

Cortical Dysplasia

Intractable epilepsy is seen in patients with unilateral multilobar or extensive cortical dysplasia. Cortical dysplasia has been

described as the most common underlying surgical pathology in children with intractable epilepsy. It is characterized by a disturbance of the normal cortical lamination, with resulting abnormal cells and neuronal circuitry that lead to increased epileptogenicity. The epilepsy type depends on the amount and location of cortical dysplasia but is usually chronic and consists of partial or generalized seizures.^{3,23}

Hemimegalencephaly

Hemimegalencephaly is a hemispheric neuronal migrational disorder. An enlarged hemisphere with lamination of only three to four layers, heterotopias, flat gyri, giant neurons, shallow sulci, poor gray-white matter differentiation, and an abnormal ventricular system characterize this disorder. Partial seizures with generalization lead to intractable epilepsy. Epileptic encephalopathy and developmental delay are the outcomes for these patients if they are not aggressively treated.^{3,22}

Rasmussen Syndrome

Rasmussen syndrome is an acquired progressive disease described as chronic encephalitis with spreading cortical inflammation that results in seizures, typically *epilepsia partialis continua*. The patients experience intellectual deterioration and progressive hemiparesis.^{3,22}

Porencephalic Cyst

Porencephalic cysts result from perinatal insults and traumatic brain injuries. Etiologies include large infarcts, intracranial hemorrhage, and coagulopathies. The epilepsy is typically medically intractable, and hemiplegia is commonly found.³

Hemiconvulsion-Hemiplegia-Epilepsy Syndrome

Hemiconvulsion-hemiplegia-epilepsy syndrome has three phases. It initially presents with unilateral, prolonged clonic seizures that affect the face, arm, and leg. This is followed by hemiplegia and partial epileptic seizures. Chronic epilepsy evolves within 1 to 2 years. The etiology of this disease is unknown.³

75.2.2 Preoperative Planning

At The Hospital for Sick Children, all patients are evaluated by an experienced pediatric epileptologist, an epilepsy surgeon, and a neuropsychologist if age permits, and they are discussed at a multidisciplinary epilepsy conference. Ancillary studies include interictal and ictal scalp video electroencephalography (EEG), magnetic resonance (MR) imaging, and frequently positron emission tomography (PET) and functional MR imaging (fMRI). Wada testing is not always feasible in children and also carries a risk for ischemia of the unaffected hemisphere.³ Patients at The Hospital for Sick Children routinely undergo magnetoencephalography (MEG). Torres et al recently reported on the contribution of MEG to patient selection for hemispherectomy. With a small cohort, they found that MEG correlated with video EEG in most patients; however, a lack of MEG spikes in

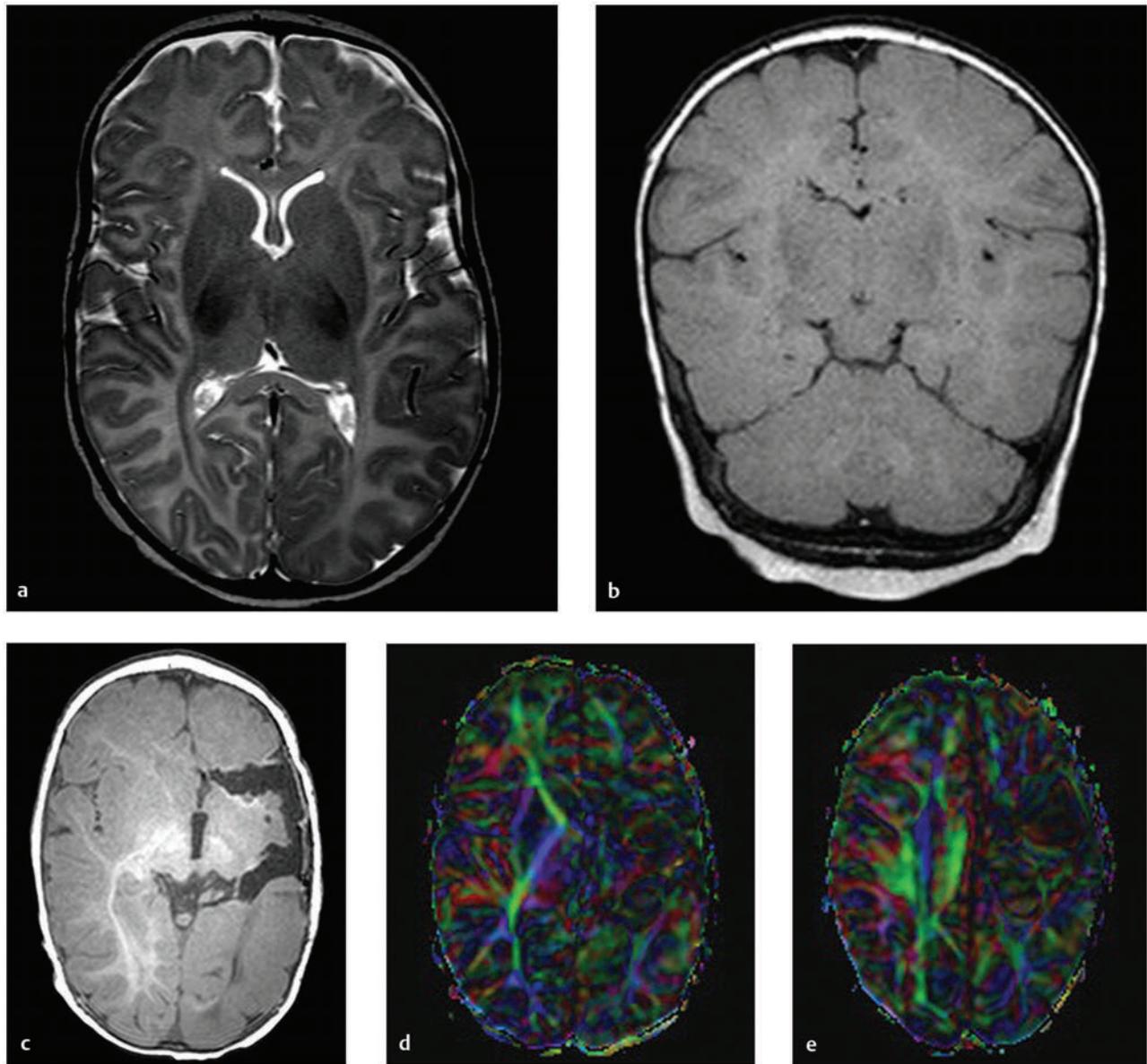


Fig. 75.1 Hemimegalencephaly. (a) Axial T2-weighted image showing thickening in the left occipital, temporal, and parietal lobes. (b) Coronal FLAIR (fluid-attenuated inversion recovery) image revealing enlargement of the left occipital and temporal lobes. (c) T1-weighted image 6 months after hemispherotomy. (d,e) Diffusion tensor imaging elucidating the functional disconnection of the left hemisphere.

the contralateral hemisphere was not a predictive factor for seizure-free outcome.²⁴ A larger cohort will likely allow further delineation of the information obtained from MEG.³

EEG will help determine if the epileptiform discharges are limited to one hemisphere. As well, predictors of good outcome are the following: ipsilateral suppression of electrical activity associated with multifocal epileptiform abnormalities confined to the damaged hemisphere; bilateral synchronous discharges spreading from the abnormal hemisphere without contralateral slowing; and the absence of generalized discharges, bilateral independent spiking, and abnormal background activity in the unaffected hemisphere. Although they do not exclude a patient from hemispherectomy, the following abnormalities in the “unaffected” hemisphere may denote an

unfavorable outcome: sporadic epileptiform discharges, abnormal secondary or independent EEG findings, and nonepileptiform abnormalities. This is especially true if independent interictal sharp wave activity is observed in the unaffected hemisphere.^{3,8}

The anatomical details gleaned from preoperative imaging to assess the feasibility of hemispherectomy include the following: ventricular size, shape and depth of sylvian fissure, location of the circular sulcus, displacement of the normal landmarks, thickness of the corpus callosum, surface anatomy, presence of parenchymal atrophy, and abnormal vasculature. It has been noted that the presence of atrophy in the ipsilateral cerebral peduncle and medulla helps to predict a lower risk for postoperative worsening.³

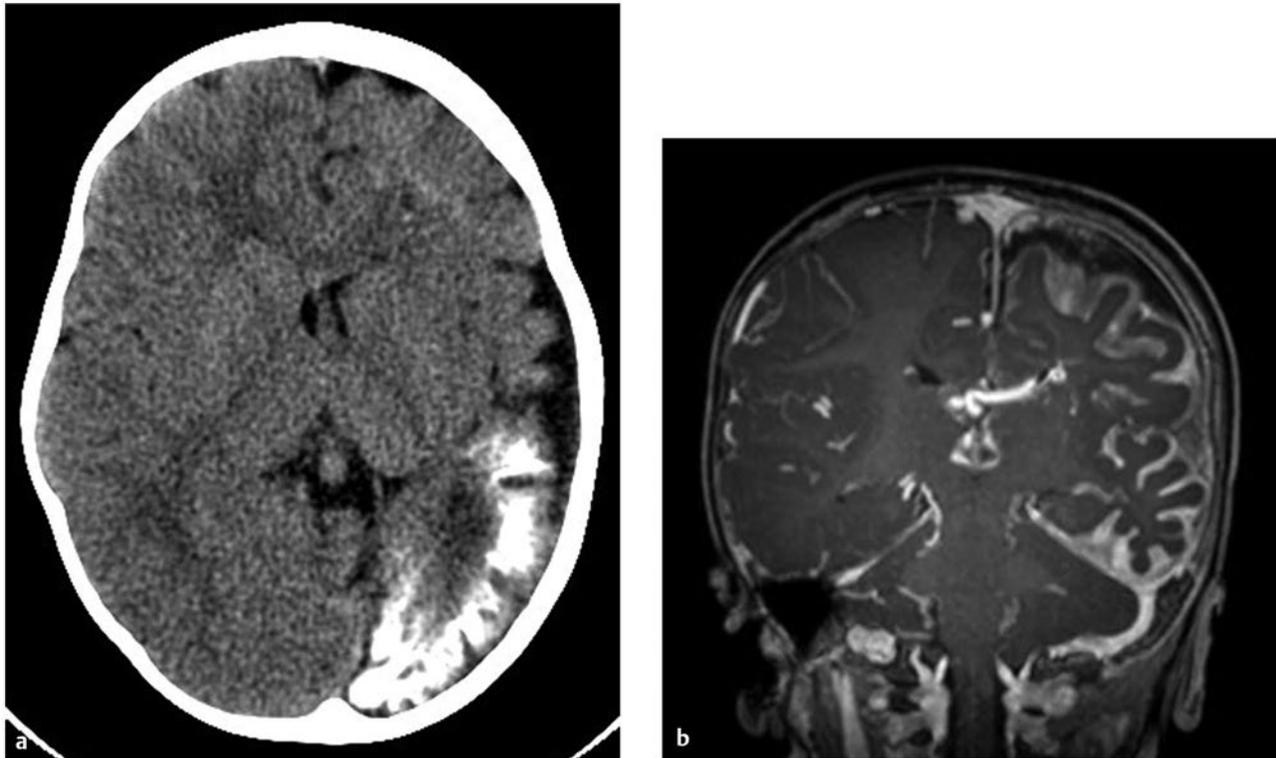


Fig. 75.2 Illustrative imaging studies depicting the neuropathology of cases for which hemispherotomy is indicated. (a,b) Axial computed tomographic scan and coronal T1-weighted magnetic resonance (MR) image with contrast of Sturge-Weber syndrome. (*continued*)

On metabolic studies, confinement of the hypometabolic and epileptogenic areas to the damaged hemisphere has been shown to be a good predictor of outcome. By the same token, if the hypometabolic areas spread into the normal hemisphere, this is an indicator of more extensive and perhaps bilateral involvement.³

75.2.3 Timing of Surgery

The ideal time for surgical intervention is debated. The goal of surgery is to protect the brain from the harmful effects of seizures and antiepileptic drugs. These effects on the immature brain, as well as the plasticity of the younger brain, argue for earlier surgery. After the sixth to eighth year, the ability of the dominant hemisphere to acquire language declines, which further supports earlier surgery. Additionally, the shorter the time between seizure onset and surgery, the higher the success rate, and earlier seizure control optimizes psychosocial development.^{3,22}

75.2.4 Techniques of Hemispherectomy

As described before, there has been an evolution from anatomical hemispherectomy to functional hemispherectomy to hemispherotomy. The difference in terminology reflects the amount of cerebral cortex resected. The anatomical hemispherectomy resects the largest amount of cortex, whereas the functional hemispherectomy combines a partial resection with a partial disconnection. Finally, the hemispherotomy resects a small amount of cortex and maximizes disconnection.⁸

Anatomical Hemispherectomy

For a description of the anatomical hemispherectomy, the reader is referred to the article of Di Rocco et al.¹¹ A question mark-type or a T-shaped skin incision can be used. An osteoplastic craniotomy can be fashioned, or a myocutaneous skin flap can be used with a standard craniotomy. The bone flap needs to be placed close to the sagittal sinus. The hemispherectomy is initiated by exposing the distal internal cerebral artery. The middle cerebral and anterior cerebral arteries are clipped and divided. Attention is then paid to the interhemispheric cleft. The medial surface of the hemisphere is retracted, and the bridging cortical veins are divided to reach the corpus callosum. The ipsilateral pericallosal artery is divided, and the callosotomy is performed from the genu to the splenium. Once the lateral ventricle is opened, the foramen of Monro is plugged.

A transventricular endypymal incision lateral and anterior to the basal ganglia is made to detach the frontal lobe from the basal ganglia. The frontal lobectomy is completed by extending the endypymal incision up to the sylvian fissure and then continuing the incision from the fissure to the midline. Next, the parietal, occipital, and temporal lobes are disconnected. The posterior cerebral artery is divided at the level of its P3 segment. The temporal stem is divided by extending the previously created endypymal incision posteriorly to the trigone area and temporal horn. After coagulation of the bridging veins, the parieto-occipital lobe is freed with the temporal lobe and can be removed en bloc or in piecemeal fashion. An amygdalohippocampectomy is performed with subpial dissection or aspiration. The

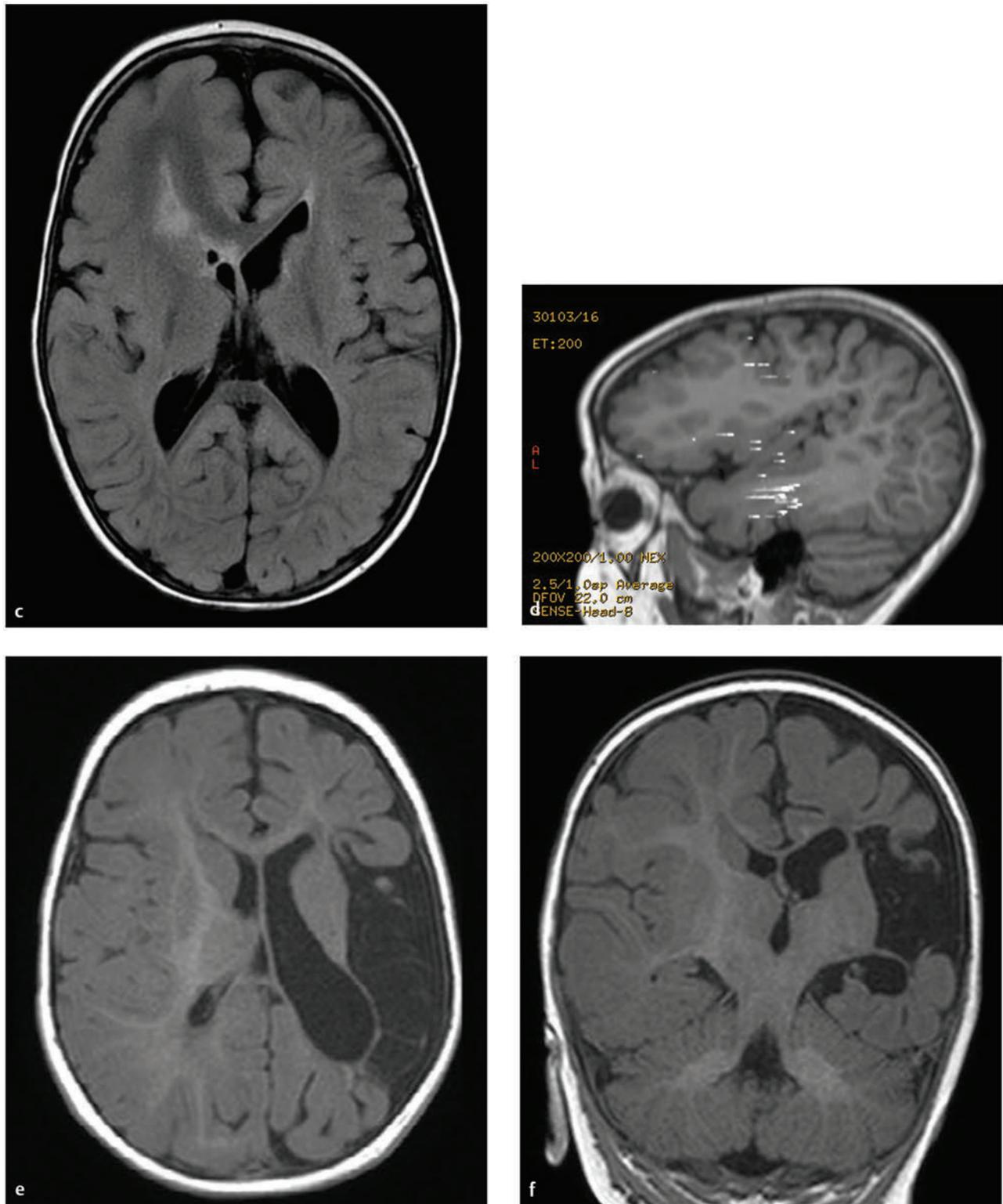


Fig. 75.2 (continued) (c,d) Axial FLAIR (fluid-attenuated inversion recovery) MR image and magnetoencephalogram of hemimegalencephaly. (e, f) Axial and coronal T1-weighted MR images of perinatal middle cerebral artery infarct.

basal ganglia are left in situ unless they are felt to be involved in the cortical malformation, with a risk for recurrent seizures.¹¹

As described previously, the Oxford modification consists of plugging the foramen of Monro and tacking the dura to the tentorium, falx, and floor of the middle cranial fossa to decrease the subdural space.⁷ As well, the Peacock addition includes routine subdural drainage with placement of a shunt in the early postoperative period.¹⁰

Functional Hemispherectomy

Rasmussen's functional hemispherectomy was the first attempt at subtotal removal with disconnection. This consists of temporal lobectomy, resection of the central region, and disconnection of the residual frontal and parieto-occipital lobes from the remaining brain, with preservation of as many arteries and veins as possible. The insular cortex is preserved unless corticography has indicated spiking, in which case a subpial resection is performed.⁹ The goal is to provide functional disconnection while preserving a large part of the brain to avoid the complications of a large surgical cavity.³

Hemispherotomy

The term *hemispherotomy* was introduced by Delalande et al in 1992 to describe minimal brain resection with maximal disconnection for intractable epilepsy.¹⁵ These procedures can be performed with a vertical or a lateral approach. Delalande and colleagues described a vertical approach. A linear transverse skin incision is made to allow a small parasagittal frontoparietal craniotomy that is based two-thirds posterior to the coronal suture and one-third anterior. A corticectomy is made to enter the lateral ventricle. A callosotomy is performed, and the posterior hippocampal disconnection is made by transecting the posterior column of the fornix at the level of the ventricular trigone. The corona radiata is transected to reach the temporal horn. An incision from the gyrus rectus to the anterior temporal horn creates the anterior disconnection.^{14,15,25} In 2001, Danielpour et al modified this technique by starting the vertical approach interhemispherically.^{3,26}

The lateral approach was described similarly by Villemure and Mascott and by Schramm et al in 1995.^{16,27} Schramm et al describe it as starting with a hippocampectomy or a hippocampectomy with an anterior temporal lobectomy. After this, deafferentation of the white matter of the temporal, occipital, parietal, and frontal lobes is performed. This can be done with a transcortical transventricular approach along the outline of the lateral ventricle. The callosotomy is performed transventricularly. A small portion of the supra-insular cortex remains, as well as the insular cortex. However, as a modification, the insular cortex can be resected. Another modification allows the entire transventricular deafferentation to be performed through a sylvian keyhole.

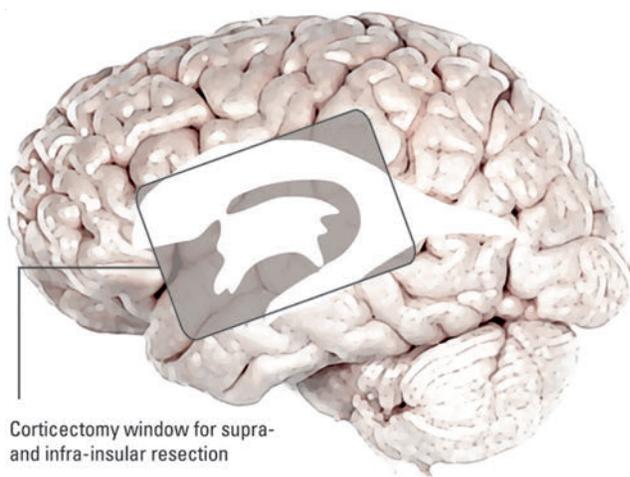
Villemure and Mascott described the technique of lateral peri-insular hemispherotomy in 1995. The authors stated it could be viewed as a "radical hemispheric tractotomy" resulting in a completely disconnected hemisphere.²⁷ The craniotomy is based over the circular sulcus and the ventricular system. The peri-insular hemispherotomy has three major surgical stages: supra-insular window, infra-insular window, and insula. In the

supra-insular window, the frontoparietal opercular cortex is resected, followed by the transection of the corona radiata and the transventricular callosotomy. The posterior hippocampectomy is completed, and the frontobasal disconnection completes the supra-insular window. The infra-insular window starts with the resection of the temporal opercular cortex, followed by the transection of the temporal stem. Next, the amygdala is resected, and the anterior hippocampectomy is completed. Finally, the insular stage consists of subpial aspiration of the insula or disconnection by incising at the level of the claustrum or extreme capsule.²⁸

There have been several modifications to the peri-insular hemispherotomy. The universal steps are disruption of the internal capsule and corona radiata, resection of the medial temporal structures, transventricular callosotomy, and disruption of the horizontal fibers.²⁹ Shimizu and Maehara introduced the transopercular hemispherotomy.³⁴ The upper half of the insula is exposed through a transsylvian approach. The arteries of the insula are coagulated and divided. Next, the frontoparietal operculum and the upper half of the insula are resected en bloc. This creates a large cavity for which the disconnection and medial temporal lobe structures occurs.^{25,29} Comair used the transsylvian approach to perform the peri-insular disconnection. This involved a vertical incision from the insula to the temporal horn, thus allowing removal of the mesial temporal lobe structures. As well, a cortical incision is made to perform the callosotomy.²⁹ Kanev et al used ultrasound to perform hemispheric disconnection without violating the ventricular cavity.³⁰ In 2004, Cook et al described the modified lateral hemispherotomy. The goal was to reduce the blood loss seen with anatomical hemispherectomy and to decrease the reoperation rate seen with the Rasmussen functional hemispherectomy. It was also postulated that it would be key for children with small or malformed ventricles. This procedure creates a working space around the ventricles by removing most of the thalamus, basal ganglia, caudate nucleus, and other associated deep hemispheric structures. These deep structures were felt to be the cause of recurrent seizures that hinder the effectiveness of functional hemispherotomy.³¹ Other recommendations have been made to limit the size of the insular window to maintain as many middle cerebral artery branches as possible.^{29,32}

At The Hospital for Sick Children, we have been using a modified peri-insular hemispherotomy approach. The patient is secured in a Sugita head holder (Mizuho, Tokyo, Japan) or a horseshoe head rest if very young. Neuronavigation is used to assist in marking the skin incision as well as localizing the ventricle. A question mark-type incision is based over the insula. A frontoparietotemporal craniotomy based on the insula is created (► Fig. 75.3). The dura is opened in a curvilinear fashion with spokes radiating superiorly, inferiorly, and posteriorly. The supra-insular window is created by resecting the frontoparietal opercular cortex down to the insular pial bank. Next, the infra-insular window is fashioned similarly to resect the temporal opercular cortex. Care is taken to preserve as many branches of the middle cerebral artery as possible to avoid remote infarcts or ischemic changes (► Fig. 75.4).

The temporal lobe is then addressed. First, the lateral neocortex is resected and sent en bloc. Next the temporal horn is entered, and a cotton square is placed in the ventricle to mark its location. The anterior temporal tip can be removed at this



Corticectomy window for supra- and infra-insular resection

Fig. 75.3 Artist's rendering of the outline of a craniotomy for exposure of the supra- and infra-insular windows.

point. Performing an anterolateral temporal lobectomy will ensure sufficient space intracranially in the event of any post-operative cerebral swelling. The hippocampus is disconnected anteriorly, mesially, and posteriorly and removed en bloc. The amygdala is also resected as part of the procedure. If a decision is made not to remove the temporal lobe, including the mesial structures, it is important to open along the length of the temporal horn and then incise the fimbria fornix at the level of the splenium of the corpus callosum so as to functionally disconnect the temporal lobe.

The corona radiata is transected by opening the temporal horn posteriorly and continuing around to the frontal horn of the lateral ventricle. To aid in the directionality of this maneuver, one can follow the course of the choroid plexus, and as the ependyma is incised, care must be taken with many of the small ependymal veins, which must be coagulated and cut sharply to control hemostasis.

The callosotomy is performed from within the exposed lateral ventricle. One of the most reliable landmarks for finding the pericallosal vessels is just posterior to the foramen of Monro and superior to the fornix just before it courses inferiorly. Careful study of the preoperative MR images and the use of neuronavigation can sometimes assist in finding the pericallosal vessels in the subarachnoid space above the corpus callosum. Once the pericallosal arteries are found, the callosotomy can be carried out anteriorly by incising the callosum along the line of the arteries (► Fig. 75.5). As the callosotomy is continued posteriorly, the pericallosal arteries often taper, so the falx can then be followed down to the tentorium. By continuing this cut along the free edge of the tentorium to the posterior hippocampal cut, the posterior hippocampal disconnection is created, and the occipital lobe is disconnected.

The frontal disconnection is created by starting at the sphenoid wing and transecting the frontal lobe in a subpial fashion to the medial interhemispheric pia, staying anterior to the basal ganglia and ventricle. This is then connected to the rostrum callosotomy by following the incision to the pericallosal arteries.

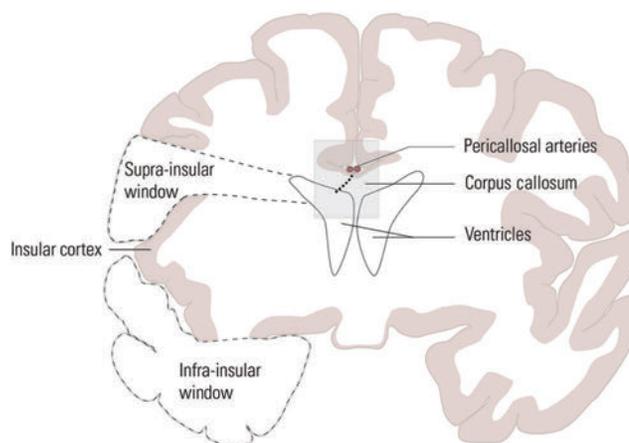


Fig. 75.4 Artist's rendering of a coronal view of the supra- and infra-insular windows and the incisions required to perform a corpus callosotomy (dotted lines).

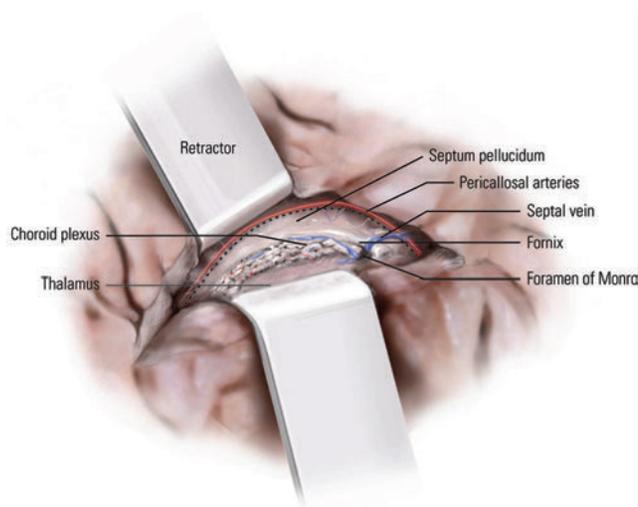


Fig. 75.5 Artist's rendering of the lateral hemisphere with focus within the lateral ventricle identifies the key landmarks for initiating a callosotomy, including the foramen of Monro, fornix, septal vein, and septum pellucidum.

Finally, the insular resection proceeds with subpial resection of the insular cortex. Again, the goal here is to preserve the many penetrating arteries that perfuse the deep gray matter structures and to remove only the cortex, which is about 3 mm in thickness.

75.3 Outcome

75.3.1 Seizure Control

Anatomical hemispherectomy can result in an 85 to 95% rate of good seizure control, defined as seizure freedom or a marked reduction in seizures.¹² Our results describing outcomes of peri-insular hemispherotomy have been previously published,

with 85 to 92% of patients having Engel class I or II outcomes.^{19, 24} These results are similar to those reported in other studies with a range of seizure control rates of 86 to 100%.^{15,19,28,33} As well, we have found better outcomes with Sturge-Weber syndrome, Rasmussen encephalitis, and focal infarct pathology, again supported in the literature.^{15,19,34}

75.3.2 Motor Outcome

Devlin et al described the clinical outcomes after hemispherectomy in 33 patients. They reported that preoperative hemiplegia remained unchanged in 67%, improved in 15%, and worsened in 18%.³⁵ Kwan et al, in a comparison of hemidecortication and peri-insular hemispherotomy, found that preoperative hemiparesis was present in 20 of 21 patients and in 16 of 20 patients, respectively. Although all had postoperative hemiparesis, 16 and 18 patients remained ambulatory.¹⁹ In the series by Kestle et al, there was no decrease in ambulatory status.³³

75.3.3 Neurocognitive and Psychological Outcome

Hemispherectomy appears to halt the progressive cognitive deterioration that is seen with catastrophic epilepsy syndromes. Devlin et al reported that the majority of patients had no further cognitive decline (23 of 33) and that 4 showed improved cognition. As well, of the 33 patients described by Devlin et al, 12 had preoperative behavioral problems. Of these, 11 significantly improved postoperatively, with 5 families reporting the resolution of behavioral symptoms. The remaining patient's behavior was unchanged.³⁵

75.3.4 Complications

Operative mortality with anatomical hemispherectomy has been reported at 1 to 7%, with the lower rate favored recently. Complications, such as cerebrospinal fluid leak, wound infection, and postoperative hematomas, parallel those in other neurosurgical procedures. However, the other common complications of blood loss and resulting anemia were the main cause of surgical mortality. Other complications included infarcts from the inadvertent contralateral clipping of vessels, brainstem distortion or edema secondary to removal of the hemisphere en bloc, hydrocephalus, and increased risk for sagittal sinus thrombosis.^{3,11} Hemispherectomy and hemispherotomy mortality rates range from 0 to 3.6%.^{12,15,33,34} The other complications are similar to those resulting from anatomical procedures; however, there is less blood loss and a decreased need for cerebrospinal fluid shunting.^{12,16,19,33} The reported rates for hydrocephalus range from 15 to 35% with anatomical hemispherectomy and from 2 to 16% with disconnective procedures.^{11,14,15,19,27}

75.4 Conclusion

Although hemispherectomy was initially developed for patients with cerebral tumors, it offers seizure freedom for patients with catastrophic epilepsy. There is a trend toward performing hemispherotomy procedures with minimal resection. However, with the anatomical modifications that can reduce the

risk for superficial hemosiderosis, hemispherectomy still holds value in selected cases in which ventricular access for a disconnection procedure is difficult because of the presence of a migrational disorder, such as hemimegalencephaly. It becomes a balance between surgical comfort with the procedure and the recognition that cerebrospinal fluid diversion may be required more frequently with anatomical procedures. Overall, as the surgical modifications continue to evolve and seizure freedom is obtained, consensus may be reached one day about which of the many procedures performed for catastrophic epilepsy in childhood holds the best promise for a good outcome and reduced morbidity.

Pearls

- Hemispherotomy can offer seizure freedom rates of 85 to 100% for patients with unilateral hemispheric intractable epilepsy.
- Commonly treated disorders include Sturge-Weber syndrome, cortical dysplasia, hemimegalencephaly, Rasmussen syndrome, porencephalic cyst, and hemiconvulsion-hemiplegia-epilepsy syndrome.
- It is imperative that all children for whom hemispherectomy or hemispherotomy is being considered undergo an evaluation by an experienced epilepsy team.
- Key anatomical details to identify on preoperative imaging include ventricular size, location of the circular sulcus, thickness of the corpus callosum, location of the pericallosal vessels, and abnormal vasculature.
- The literature supports performing surgery at an early age because of the plasticity of the younger brain.
- The key steps of a peri-insular hemispherotomy include supra- and infra-insular windows, temporal lobectomy, transection of the corona radiata, callosotomy, frontal disconnection, and insular resection.

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76 Spasticity and Movement Disorders

A. Leland Albright

Although thousands of children have spasticity or other movement disorders, few pediatric neurosurgeons are involved in their care. That under-involvement partially reflects the paucity of neurosurgical treatments that were available historically. Until 1987, when Warwick Peacock and colleagues popularized selective dorsal rhizotomies,¹ pediatric neurosurgeons had little to offer children with spasticity. Since 1987, several methods for treating spasticity have become available, including oral medications (tizanidine), intramuscular (IM) medications (botulinum toxins), intrathecal medications (baclofen), and nonselective rhizotomies. Surgical options for treating dystonia and other movement disorders have increased with the introduction of intrathecal baclofen and deep brain stimulation. These options allow pediatric neurosurgeons to become involved in the care of a large group of children with whom we previously had minimal involvement, children whose quality of life can often be improved substantially.

The under-involvement of pediatric neurosurgeons in the care of children with spasticity or other movement disorders may also reflect a preference for not being involved in the treatment of severely disabled children and an uncertainty about how best to treat these complex patients. Much of their complexity is due to the fact that they often have more than one movement disorder; combinations of spasticity and dystonia, or of chorea and athetosis, are common, particularly in children with cerebral palsy (CP), and the most frequent cause of movement disorders in children is CP. Video examples of pediatric movement disorders are available on the WeMove Web site, <http://www.wemove.org>.

76.1 Spasticity

A task force defined spasticity as hypertonia in which one or both of the following signs are present: (1) resistance to externally imposed movement that increases with increasing speed of stretch and varies with the direction of joint movement, and/or (2) resistance to externally imposed movement that rises rapidly above a threshold speed or joint angle.² Clinically, spasticity may be defined as a velocity-dependent, increased resistance to passive muscle stretch. Strictly speaking, spasticity does not cause sustained, tonic increases of muscle tone, but rather increases in tone that vary according to movement, alertness, pain, and anxiety of the patient. Spasticity may be considered an isokinetic movement disorder because the amount of movement is not increased, as it is in hyperkinetic disorders like dystonia and chorea.

Spasticity is classified according to the limbs affected: spastic quadriplegia if all extremities are affected; spastic diplegia (or spastic paraparesis—the terms are synonymous) if the lower extremities are involved; spastic hemiparesis if an ipsilateral arm and leg are involved; and spastic monoparesis if only one limb is affected. Spasticity can affect trunk and cervical muscles, but no classification system grades their involvement. In Europe, children with spasticity that affects all extremities equally are said to have spastic tetraplegia, whereas those with more

severe involvement of the lower extremities than the upper are said to have spastic diplegia.

Spasticity has enormous clinical and economic implications. If untreated, it leads to progressive disability, discomfort, and deformity, and to multiple orthopedic operations to correct the deformities.

76.1.1 Epidemiology

Spasticity is common. It occurs in approximately 60% of individuals with CP (which occurs in 2.5 of 1,000 live births) and thus affects some 300,000 individuals younger than 18 years in the United States. The incidence of CP is not declining in the United States, probably because of the increased survival of low-birth-weight infants; the risk for CP is increased 25 to 30 times for those weighing less than 1,500 g.³ Spasticity also occurs in substantial numbers of children after serious head injuries and strokes, but the number with spasticity from those causes is unknown.

When spasticity occurs in association with CP, it is often not identified until 1 year of age or more. It may be more severe in the first 2 to 3 years of life, then improve as myelination increases. In a landmark study, Nelson and Ellenberg⁴ found that approximately two-thirds of children in whom spastic diplegia was diagnosed—and half of all children in whom CP was diagnosed at their first birthday—“outgrew” or lost the motor signs of the CP by their seventh year. Spasticity in CP may improve over time, and it does not worsen, although it may appear to do so for three reasons: increasing muscle strength, worsening contractures, and misdiagnosis (when worsening hypertonicity is due to dystonia rather than to spasticity). Spasticity that occurs in the first months after severe head injury is particularly likely to improve, so that permanent treatments, such as neurectomies, are infrequently appropriate during that year (although reversible treatments, such as botulinum toxin injections and intrathecal baclofen, may be appropriate).

76.1.2 Pathology and Pathophysiology

The pathophysiology of pediatric movement disorders was reviewed by Sanger in 2003.⁵ Muscle tone (the state of muscle contraction) is regulated by output from α motor neurons and is influenced by competing impulses: excitatory impulses, which enter the spinal cord via type Ia afferents from muscle spindles and cause the release of excitatory neurotransmitters, such as glutamate and aspartate; and descending inhibitory impulses from the basal ganglia and cerebellum, which cause the release of the inhibitory neurotransmitter γ -aminobutyric acid (GABA).⁶ Spasticity in humans is not due to increased gain of the muscle spindle, increased excitation of type Ia afferents, or increased γ efferents. There is probably reduced reciprocal inhibition of antagonistic motor pools by Ia afferents and decreased nonreciprocal inhibition by Ib terminals.⁷ Spasticity that develops in childhood differs somewhat from spasticity that develops in adults; early central nervous system (CNS) injury seems

more likely to result in a reorganization of corticospinal projections that leads to co-activation of agonist and antagonist muscle groups.^{8,9}

In simplistic terms, virtually all spasticity—whether of cerebral or spinal origin—can be attributed to an imbalance of excitatory and inhibitory impulses, with a relative deficiency of GABA in the spinal cord because of injury either to the developing brain or to the spinal cord conducting the descending inhibitory impulses. This pathophysiologic model also suggests two potential treatments: reducing the afferent excitatory input by rhizotomy and increasing the inhibitory neurotransmitter with a GABA agonist, such as baclofen. The paradigm also gives rise to the postulate that descending inhibitory impulses might be increased by cerebellar or spinal cord stimulation with implanted electrodes, treatments that were not effective.^{10,11}

76.1.3 Clinical Features and Grading

Symptoms of spasticity include muscle stiffness and tightness, fatigability, and pain. Pain often occurs during the night as a result of lower extremity muscle cramps or the inability to change positions. Spasticity in proximal lower extremity muscles causes progressive hip dislocation, which leads to acetabular deformity; this in turn may later cause intractable hip pain.

Spasticity typically involves certain muscles more than others; flexors and internal rotators are affected more than their antagonists. For children with spastic quadriplegia, that pattern of involvement results in the common stance of flexion at the elbows and wrists, with the child standing on the toes, the knees and hips somewhat flexed, and the legs internally rotated.

Spasticity associated with spinal cord injuries differs from cerebral spasticity in two ways: it is typically more severe because more descending inhibitory impulses are abolished, and it is more likely to be associated with painful muscle spasms. After spinal cord injuries, Ashworth Scale scores of 4 to 5, severe clonus, and muscle spasms are typical, whereas scores of 3 to 4 and less severe clonus are seen in cerebral spasticity. Clonus may be present at the ankle or knee and may occur spontaneously.

On examination, spasticity is usually evident exactly as it is defined, as a velocity-dependent, increased resistance to passive muscle stretch, so that as a joint is passively moved at vary-

ing rates, resistance varies. Spasticity is graded most commonly with the Ashworth Scale or Modified Ashworth Scale (► Table 76.1), based on the subjective grading of resistance to passive muscle stretch. Interrater reliability of the scale has been demonstrated.¹⁵ A less common method of evaluating tone is with the Tardieu Scale, although it is thought to provide a more accurate assessment than the Ashworth Scales (► Table 76.2).¹⁶ Spasticity is usually assessed with the child lying down, although a few children have dynamic spasticity, in which their tone is normal when they are lying down but increases when they stand or walk, especially tone in the adductors and plantar flexors.

When a child with spasticity is evaluated, it is important also to test the strength of the affected muscles because some children supplement weak voluntary muscle contractions with the involuntary muscle contractions of spasticity, so that gait and pivot transfers may worsen if spasticity is reduced. In children with spastic lower extremities, leg strength can be assessed by having them rise from a sitting position on a stool, by having them squat and rise in increments, and by having them stand on one foot at a time (Trendelenburg test); pelvic tilt to the lifted side indicates hip abductor weakness of the leg they are standing on.

If a muscle is affected by spasticity for several months, the muscle and its tendon undergo a permanent shortening—a musculoskeletal contracture—which is a fixed deformity that does not improve after treatment of the spasticity. Ideally, spasticity should be treated early to prevent the development of contractures, which occur most commonly in muscles that are affected most by spasticity: foot plantar flexors, knee flexors, and hip adductors.

Pediatric neurosurgeons who treat children with CP occasionally encounter some with hereditary spastic paraparesis (Strümpell-Lorrain disease), which is often misdiagnosed as CP.¹⁷ Hereditary spastic paraparesis is characterized by no history of perinatal asphyxia, normal intellect, slightly delayed motor milestones, and slowly progressive spastic paraparesis. A careful family history often uncovers symptoms in family members, although the extent of involvement may vary considerably from member to member. Neurosurgeons are also asked to see children in whom spastic CP has been misdiagnosed, but who have dystonia.

Table 76.1 Spasticity Scales

Ashworth Scale		Modified Ashworth Scale	
Score	Degree of muscle tone	Grade	Description
1	No increase in muscle tone	0	No increase in muscle tone
2	Slight increase in muscle tone, giving a “catch” when affected part is moved in flexion or extension	1	Slight increase in muscle tone
3	Moderate increase in muscle tone, passive movement difficult	1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
4	Considerable increase in muscle tone, passive movements difficult	2	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved
5	Affected part rigid in flexion or extension	3	Considerable increase in muscle tone, passive movement difficult
		4	Affected part(s) rigid in flexion or extension

Table 76.2 Tardieu Spasticity Scale

Velocities	
V1	As slow as possible, slower than the natural drop of the limb segment under gravity
V2	Speed of limb segment falling under gravity
V3	As fast as possible, faster than the rate of the natural drop of the limb segment under gravity
Scoring	
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of the passive movement, no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by release
3	Fatigable clonus with less than 10 seconds when the pressure is maintained and appearing at the precise angle
4	Unfatigable clonus with more than 10 seconds when the pressure is maintained and appearing at a precise angle
5	Joint immobile

Note: This test is performed with the child in the supine position, with the head in midline. Measurements are taken at three velocities: V1, V2, and V3. Responses are recorded at each velocity as X/Y, with X indicating the 0 to 5 rating and Y indicating the angle (in degrees) at which the muscle reaction occurs. If the limb is moved at different velocities, the response to stretch can be more easily gauged because the stretch reflex responds differently to changes in velocity.

76.1.4 Diagnostic Studies

No computed tomographic (CT) or magnetic resonance (MR) imaging characteristics are pathognomonic for spasticity, although MR images of children with spastic diplegia frequently demonstrate periventricular leukomalacia (► Fig. 76.1), and those of children with spastic quadriplegia often demonstrate multifocal, cystic encephalomalacia that involves both the cortex and underlying white matter. Neuroimaging features of spasticity and other movement disorders have been described.¹⁸

No methods are widely available to quantitate spasticity. Thus far, neurophysiologic techniques, such as H-reflex excitability curves and devices to measure velocity, joint angle, and torque, have not gained widespread clinical use. Electromyograms do not quantitate spasticity. In gait analysis studies, electrodes are applied to multiple lower extremity muscles; joint markers are applied to the hips, knees, and ankles; and children are videotaped while walking. Gait analysis allows a determination of which muscles contract during the gait cycle (frequently

identifying the simultaneous contraction of agonists and antagonists), stride length, cadence, and joint angles during the gait cycle. The interpretation of gait analysis is complex, but the resultant information is often helpful in planning subsequent orthopedic and neurosurgical intervention in ambulatory children. A complete discussion of gait analysis is beyond the scope of this chapter but is available in a publication.¹⁹

76.1.5 Treatment

It is important to remember that not all spasticity needs to be treated; spasticity that is mild, functionally useful, and neither interfering with function nor causing contractures can be left alone. If spasticity is to be treated, the treater and the treated should agree on the treatment goals. Common goals are to (1) improve function, (2) facilitate care, (3) retard or prevent the development of contractures, and (4) reduce or prevent pain. Patients commonly, and not unexpectedly, have higher hopes and expectations of treatment than do the treating physicians, despite careful preoperative discussions.

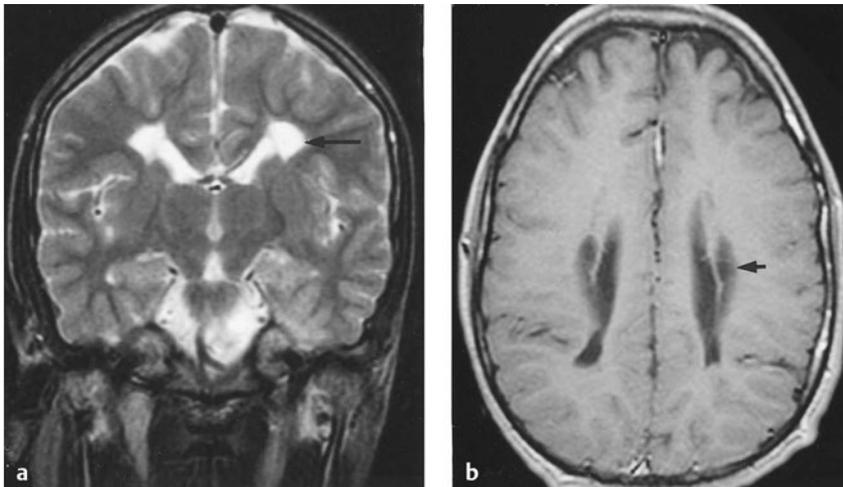


Fig. 76.1 (a) Axial and (b) sagittal magnetic resonance images demonstrating periventricular leukomalacia in a pediatric patient with spastic diplegia.

Spasticity can be treated with oral medications, intramuscular injections, intrathecal medications, and neurosurgical operations. The plethora of treatment options increases the dilemma for parents and patients and, to some degree, for physicians. Few centers have experience with all treatment modalities. Almost no good-quality studies have been done to evaluate the results of individual treatment modalities, much less to compare one modality with another. Ideally, children with spasticity should be evaluated in a multidisciplinary clinic that has experience in all treatment modalities. A gross motor function classification system (GMFCS) has been developed to classify function in children with CP so that the effects of treatments can be more readily compared.¹⁹

Treatment selection also varies according to the severity of the spasticity, the extent of the muscles involved, the age of the child, and the therapeutic goals, as discussed later. ▶ Table 76.3 lists the common treatments and their general indications.

Oral Medications

Three oral medications are thought to be useful in treating pediatric spasticity: baclofen, diazepam, and dantrolene^{12,20}; all act systemically and decrease spasticity diffusely. No study has compared their effectiveness, which is usually mild and often seems to wane over a few years. Medication dosages are listed in ▶ Table 76.3. For each medication, doses are adjusted to obtain the greatest therapeutic benefit with the fewest side effects. The use of oral medications for treating spasticity has been reviewed recently.²²

Baclofen (Lioresal; Novartis Pharmaceuticals, East Hanover, NJ), or chlorophenol GABA, is a GABA agonist that was synthesized to be an anticonvulsant (its antiepileptic activity was minimal). It is absorbed well and rapidly from the gastrointestinal tract, with peak serum levels 2 hours after a dose. The serum half-life is 3 to 4 hours. Baclofen is a racemic mixture whose site of action is the spinal cord, where primarily the levo-enantiomer acts both to decrease the release of excitatory neurotransmitters from type Ia fibers in superficial (Rexed layers I and II) layers of the spinal cord and to reduce postsynaptic impulses. Baclofen crosses the blood-brain barrier poorly; oral doses of 60 to 90 mg/d are usually associated with serum levels of 68 to 650 ng/mL, but with cerebrospinal fluid (CSF) levels of 12 to 95 ng/mL.²³ In a double-blinded crossover study of 15 children with spasticity and GMFCS levels of IV or V, children receiving baclofen scored significantly better on the goal attainment scale than those receiving placebo.²⁴

Diazepam (Valium; Roche Pharmaceuticals, Nutley, NJ) is a benzodiazepine receptor agonist that is also absorbed well and rapidly after oral administration. It crosses the blood-brain barrier moderately well and attaches to GABA_A and GABA_B receptors in the brain and spinal cord, so that it has a higher frequency of CNS side effects. Its half-life is 36 hours. It improves spasticity of children with CP, but effective doses frequently cause unacceptable sedation.²⁵ Dependence may develop after chronic administration, so that the drug should be discontinued slowly, often over months.

Tizanidine (Zanaflex; Acorda Therapeutics, Ardsley, NY), an α_2 -agonist, appears to modulate the release of excitatory neurotransmitters from interneurons and afferent terminals. Tizanidine was approved for the treatment of spasticity based on the

results of clinical trials of adult patients with spasticity from spinal cord injury or multiple sclerosis, in whom its effectiveness appeared to be similar to that of baclofen. A multicenter study of tizanidine in children with spasticity secondary to cerebral spasticity was recently concluded; the results have not been published as of September 2013.

Modafinil (Provigil; Cephalon, Frazer, PA) is a centrally acting stimulant that is thought to stimulate anterior hypothalamic nuclei. It was reported to improve spasticity in children with CP, but a subsequent double-blinded crossover study found that modafinil did not reduce spasticity or have a positive effect on quality of life.²⁶

Dantrolene (Dantrium; Procter & Gamble Pharmaceuticals, Cincinnati, OH) is the only medication to act at a non-CNS site, the sarcoplasmic reticulum, where it prevents the calcium influx necessary for muscle contraction and thus is less frequently associated with drowsiness or other CNS side effects. Its peak activity is 4 to 8 hours after administration. Although dantrolene has been reported to cause hepatotoxicity, usually after 3 to 12 months of treatment, severe hepatotoxicity rarely occurs in children younger than 10 years old, and fatal hepatotoxicity has not been reported in patients younger than 20 years old.²⁷

Baclofen is usually the first choice of oral agents. Doses are increased until improvement occurs, unacceptable side effects occur, or the maximum dose recommended for body weight is reached. If spasticity cannot be treated effectively with baclofen, it probably cannot be treated with other available agents used singly. Diazepam or dantrolene is occasionally given in combination with baclofen. Data comparing monotherapy with combination therapy are not available.

Neuromuscular Blockade

Neuromuscular blockade can be used to weaken muscle contractions, and thus spasticity, by interfering with nerve transmission, the neuromuscular junction, or muscle contraction. Medications available for IM injection include the following: botulinum toxin serotype A (Botox [Allergan, Irvine, CA]; Onabotulinumtoxin A—a purified version containing no extraneous proteins [Allergan]; Dysport [Ipsen, Slough, UK]); botulinum toxin serotype B (Myobloc; Solstice Neurosciences, South San Francisco, CA); phenol; and alcohol.^{28,29} No studies have compared their effectiveness. None treats spasticity per se; rather, they weaken the contraction of the injected muscle. IM injections are most appropriate for spasticity that affects localized muscle groups (e.g., plantar flexors and adductors) and are not appropriate treatment for generalized spasticity. However, for children with generalized spasticity, IM injections into the most severely affected muscles can be combined with oral medications that treat less involved muscles. Because the effects of IM medications usually wear off in a few months, such injections must be repeated and rarely provide a definitive treatment of spasticity. They are given with several goals: to decrease the spasticity of certain muscles (e.g., adductors) so that physical therapy can strengthen the antagonist muscles (abductors), to facilitate the serial casting of joints, and (rarely) to help determine if function of a limb would improve if spasticity were reduced. The use of injectable neuromuscular blockade to treat spasticity and other movement disorders was recently reviewed.^{30,31}

Table 76.3 Treatments for Spasticity

Method	Age (y)	Diagnosis	Characteristics	Expected results	Follow-up care	Outcome	Side effects, risk
Oral medications	Any age, most often 2 to 5	Spastic quadriplegia, traumatic brain injury	Diffuse spasticity	Mild decrease in spasticity in arms and legs	PT, OT as needed	SPRs or ITB often needed later	Drowsiness
Botox injections	Any age, less often older than 10	Spastic diplegia, spastic quadriplegia	Isolated spasticity; too young for ITB, SPRs	Decrease in spasticity in injected muscle(s) for 2 to 4 months	PT, OT to increase range of motion and to increase strength	Improved gait, sometimes improved arm function	None with usual doses
Rhizotomy (SPRs)	4 to 8 (most common), rare after 16	Spastic diplegia or quadriplegia, <i>capable</i> of ADLs	Good leg strength, no severe contractures, motivation for PT	Marked, permanent, nonadjustable decrease in spasticity	Extensive PT, OT	Improved walking, improved ADLs, decrease in orthopedic operations	Infection, 2%; wound, 1%; CSF leak, 3%
	Older than age 3, before multiple contractions	Spastic diplegia or quadriplegia, <i>not capable</i> of ADLs	Severe leg spasticity interfering with care		Minimal	Easier care	Infection, 2%; wound, 1%; CSF leak, 3%
Baclofen (ITB)	Older than age 3, big enough to insert pump	Spastic quadriplegia, spasticity in legs greater than or equal to spasticity in arms, <i>capable</i> of ADLs	Severe spasticity, positive response to test dose, spasticity limiting function	Adjustable decrease in spasticity	Frequency of PT, OT depends on goals	Improved walking, improved ADLs, improved speech, decrease in orthopedic operations, easier care	Infection, 5 to 10%; wound, 5 to 10%; CSF leak, 5 to 10%
		Spastic quadriplegia, <i>not capable</i> of ADLs	Spasticity interfering with care		Minimal PT	Easier care	
		Posttraumatic brain injury	Severe spasticity in arms or legs, usually more than 1 year after injury		PT, OT for range of motion		

Abbreviations: ADLs, activities of daily living; CSF, cerebral spinal fluid; ITB, intrathecal baclofen; OT, occupational therapy; PT, physical therapy; SPRs, selective posterior rhizotomies.

Botulinum toxin acts at the neuromuscular junction to prevent the release of acetylcholine. There are seven botulinum neurotoxins (A through G), two of which are commercially available. Botox is type A, the most potent serotype; Myobloc is type B. Botox is injected directly into muscle; its effect commences within 1 to 3 days, is maximal at 21 days, and wanes—perhaps because of the development of new neuromuscular junctions—by 3 to 4 months afterward, when the injections can be repeated. Doses depend on the size of the muscle to be injected and on the severity of its spasticity. In the lower extremities, Botox is often injected into spastic gastrocnemius, hamstring, and adductor muscles. If injections are needed into muscles that are difficult to locate by palpation, such as the pronator teres or posterior tibial muscle, electrical stimulation will identify the desired injection site.

The maximal recommended Botox dose at present is 10 U/kg, although I, and others, have used 20 to 25 U/kg without adverse effects. The drug comes as a precipitate in vials of 100 U, is diluted to 10 U/0.1 mL or 10 U/0.2 mL, and injected into muscles at one to several sites. Dysport, the form of botulinum toxin available in the United Kingdom, is now available in the United States. It has approximately one-third the potency of Botox, and doses are accordingly higher.

The effects of Botox—alone or in combination with occupational therapy—on the upper extremities of children with spastic CP were evaluated in a 2010 Cochrane Systematic Review of 10 randomized controlled trials (RCTs).³⁰ The combination of Botox and occupational therapy was more effective than occupational therapy alone in reducing impairment and improving activity-level outcomes, but not for improving quality of life. There was moderate evidence that the use of Botox alone was not effective. The effects of Botox on lower extremity spasticity and gait have been evaluated in recent reviews of RCTs. Boyd and Hays reviewed 10 RCTs and concluded that Botox had a moderate, dose-dependent effect on gait and lower limb function.³¹ Koog and Min reviewed 15 RCTs and concluded that botulinum toxin serotype A (BtxA) was little better than a sham control.³² Ryll et al reviewed 8 RCTs that compared BtxA plus usual care or physiotherapy versus physiotherapy alone.³³ The studies showed moderate evidence for improved functional outcomes—mainly walking—at 2 to 24 weeks for those receiving BtxA, but no difference between BtxA and casting. BtxA treatment of ambulatory children with spastic CP has been shown to improve gait analysis parameters and to reduce oxygen consumption.³⁴

Treatment with IM injections provides temporary improvement of spasticity and thus may be considered as a bridge to more definitive treatments. I often use Botox repeatedly in patients from age 2 years until age 5 or 6 years, by which time it is usually apparent whether the child will need longer-term treatment, such as a rhizotomy or an intrathecal baclofen pump. Only a few children who are treated with Botox in the 2- to 5-year interval improve enough that no subsequent intervention is needed. Children almost never develop immunity to Botox; the preparations that have been available in recent years are more purified and lack the protein to which early subjects occasionally developed antibodies.

Botox is tightly bound to the neuromuscular junction and a minimal amount enters the systemic circulation, so that systemic side effects are uncommon after injections into extremity

muscles. Those effects include flulike symptoms, generalized weakness, dysphagia, and aspiration. In 2008, the Food and Drug Administration (FDA) reported that children treated for spastic CP had rarely developed serious side effects consistent with botulism.³⁵ In a subsequent meta-analysis of 20 RCTs and 882 subjects who had received BtxA, a variety of symptoms were reported, including muscle weakness, urinary incontinence, fever, falls, and pain.³⁶ Two deaths were reported but were thought to be unrelated to BtxA, and the authors concluded that BtxA had a good short-term safety profile. Despite the FDA warning, the use of BtxA remains widespread.

One circumstance in which Botox injection is probably underused is in children with severe head injury in whom gastrocnemius spasticity causes severe plantar flexion of the feet within weeks after injury. The plantar flexion is usually treated ineffectively by serial casting, and children typically develop plantarflexion contractures that require orthopedic releases. Posttraumatic spasticity often abates within 6 to 12 months, but by then, contractures have developed. The injection of BtxA into the affected muscles early after injury, as soon as significant spasticity is detected, should minimize such contractures, particularly if combined with ankle casting.

Phenol and alcohol can be injected directly into spastic muscles, where they cause focal muscle necrosis, or at the myoneural junction. Injections are painful, cause muscle soreness for several days, and are usually performed in children under a brief anesthetic. IM injections of 50% alcohol, 5 mL at one to three sites, or perineural injections of 5% aqueous phenol are common. Weakness of the injected muscle develops over several days and persists for weeks to months. Because of the pain and dysesthesias associated with their use and the variable responses obtained, phenol and alcohol are used much less frequently since the availability of Botox. However, because alcohol and phenol are far less expensive than Botox, and their effects persist longer, they are preferred in some centers to treat spastic muscles innervated by motor nerves, and they remain the injectable option of choice in developing countries.

Intrathecal Medications

Intrathecal baclofen (ITB) is by far the most common medication to be infused intrathecally, although morphine, fentanyl, tizanidine, and clonazepam have been used.

ITB is more effective than oral baclofen because the CSF concentration of baclofen obtained after intrathecal injection is so much higher than that after oral administration (400 ng/mL in a patient receiving 396 µg of ITB per day versus less than 12 ng/mL in a patient receiving 60 mg of oral baclofen per day).²³ After a single ITB dose, spasticity in the lower extremities begins to diminish in 2 hours, is maximally reduced in 4 hours, and recurs in 8 to 10 hours.³⁷ The half-life of an intrathecal dose is 4 to 5 hours.³⁸ ITB is cleared at a rate of 30 mL/h, the rate of CSF clearance. After baclofen infusions in the region of the conus medullaris, lumbar CSF concentrations are approximately fourfold higher than those at the cisterna magna.³⁹ These data suggest that the position of the catheter tip should vary according to whether spastic diplegia or quadriplegia is being treated.

ITB is effective in treating spasticity of spinal or cerebral origin. It diminishes stretch reflex excitability and abnormal muscle co-contractions that occur in children with cerebral

spasticity.^{40,41} ITB has been used to treat children and adolescents with spinal spasticity due to trauma, transverse myelitis, arteriovenous malformations, or familial spastic paraparesis.⁴²

We conducted a prospective study of long-term ITB in 37 children with cerebral spasticity that was mostly due to CP but also due to head injury or ischemia.⁴³ We found that ITB reduced spasticity in the lower and upper extremities and that improvement occurred in hamstring range of motion and in position transitions. Improvement was also noted on an activities-of-daily-living scale that assessed communication, dressing, positioning, and feeding. Since then, multiple studies have confirmed the effectiveness of ITB in reducing spasticity, in improving motor function as evaluated by the Gross Motor Function Measure (GMFM), and in improving comfort and caregiving.^{44–46}

Until recently, a test dose of ITB was always given to confirm the child's response to ITB before a pump was implanted. As hundreds of children have been tested with bolus injections, it has become apparent that almost all respond to the bolus doses if they have spasticity (but not dystonia or contractures). Additional reasons not to do a test dose are that the customary doses, 50 to 100 µg, are excessive and result in extreme hypotonia of the lower extremities, in addition to the headache and vomiting that commonly occur after lumbar puncture. Thus, increasing numbers of centers that have experience with bolus doses and patient selection are forgoing the test injections and proceeding directly to pump implantation.

In children with spasticity and ventriculomegaly who may need a pump, it is important to consider a lumbar puncture to measure the opening pressure before a pump is inserted. Many children with spastic CP have had intraventricular hemorrhages as infants and have chronic ventriculomegaly and increased opening pressures.⁴⁷ If such pressure is not addressed, it increases the risk for CSF leaks around the intrathecal catheter if a pump is subsequently implanted.

ITB is usually administered by a programmable pump implanted subcutaneously or subfascially in the abdomen and connected to a catheter that is tunneled subcutaneously posteriorly to the lumbar region, then via a Tuohy needle into the CSF. Nonprogrammable pumps are available but do not allow the frequent dose adjustments that are needed in the first 1 to 2 years when cerebral spasticity is being treated. Pumps are programmed to deliver doses of baclofen that are adjusted according to the goals of treatment. SynchroMed II pumps (Medtronic, Minneapolis, MN) have 20- or 40-mL reservoirs. The 20-mL pump is small enough to be inserted into children weighing 10 kg. When pumps are implanted into small, thin children, healing appears to be better if the pumps are implanted below the abdominal fascia.

The main risks of pump implantation are infection, CSF leakage, and catheter problems, such as breaking and cracking.⁴⁸ The risk for each is approximately 5 to 10%. Borowski et al reported a 31% complication rate requiring surgical management over a 3-year period in 316 surgical procedures.⁴⁹ If a pump infection occurs, some neurosurgeons have attempted to "save" the system by irrigating or debriding the wound and giving intravenous antibiotics for 2 to 3 weeks. In my experience, the likelihood of success with that technique is small.

ITB doses typically increase during the first year after implantation, then remain relatively stable. If a child has had good

results from ITB for 1 to 2 years and then the effects wane despite increasing doses, there is almost always a problem with the catheter infusion system, not the pump. The current Medtronic pump battery lasts approximately 7 years before replacement is necessary. After a child has received ITB for several months, it should not be withdrawn abruptly. Withdrawal symptoms of itching, agitation, and spasms are common; seizures and fever may occur; and severe symptoms, such as hyperthermia, psychosis, and multiple-organ failure, have been reported.^{50,51} Children presenting with signs and symptoms of ITB withdrawal must be given large doses of oral baclofen, evaluated urgently, and have the malfunction repaired promptly.⁵²

Side effects of ITB include listlessness, hypotonia of the trunk and neck, and occasional urinary hesitancy, symptoms that subside with reduction in dosage. ITB does not appear to increase the frequency of seizures. In a multicenter study of ITB in 68 children, seizure frequency was increased in none of the children.⁵³ Overdoses, which are rare during routine treatment, cause profound muscle hypotonia and lethargy. Treatment of severe overdoses includes artificial ventilation, stopping the pump, and CSF barbotage. The drug is not toxic, and ITB infusion usually resumes after the overdose clears in 1 to 2 days.

Advantages of ITB therapy are that it is highly effective in reducing spasticity in the arms and legs and often improves global function. Furthermore, the dose can be titrated to obtain the desired reduction in spasticity, and ITB is nondestructive. Its disadvantages are the costs of the pump, implantation, and refills, and the complications of the infusion system.

Rhizotomies

Ventral (motor) rhizotomies were described for adults with spasticity in 1932, but they fell out of favor because of muscle atrophy and the resultant loss of function.⁵⁴ They have no place in the current treatment of pediatric spasticity. The neurophysiologist Sherrington⁵⁵ laid the foundation for dorsal rhizotomies. He treated the "spasticity" that resulted after sectioning the midbrain of cats with rhizotomies of the cervical dorsal roots and found that their hypertonia was abolished. Parenthetically, they probably had extensor rigidity rather than spasticity. Based on that laboratory work, Foerster⁵⁶ performed L2–S1 rhizotomies, sparing L4, in 153 children with cerebral spasticity and reported excellent results. The procedure was not used thereafter for several decades, probably because of the sensory loss and ataxia that would occur if the entire sensory roots of L2, L3, L5, and S1 were divided.

In 1978, Fasano et al⁵⁷ reported their use of selective dorsal rhizotomy (SDR). They stimulated the lumbar posterior roots of children with CP at various rates (1 to 50 Hz) and found that the stimulation of "normal" roots at 50 Hz caused a brief muscle contraction followed by relaxation, but that stimulation of "abnormal" roots caused a tetanic contraction that often persisted after the stimulus ceased. They divided the rootlets that generated the "abnormal" response and reported good relief of lower extremity spasticity in 71% of cases, with return of spasticity in approximately 5% of cases in the following years. This procedure was modified and popularized by Peacock et al, who identified as "abnormal" features tetanic responses, responses that persisted after the stimulus ceased, clonus, contraction of muscles in the contralateral extremity, and contraction of

muscles not normally in that myotome.¹ They also performed the testing and division of the nerves at their exit zones from the dural sac, where they could be identified more readily than at the point where they entered the conus medullaris. Park and Johnston subsequently advocated dorsal rhizotomies at the conus, via limited laminotomies, and reported equally good outcomes.⁵⁸ Ou et al compared outcomes after single-level laminotomies at the conus versus multilevel lumbar laminectomies and found no differences in outcomes other than shorter hospitalizations after the single-level procedure.⁵⁹

There is continued controversy about the validity of the neurophysiologic criteria used to distinguish normal and abnormal responses. It appears that tetanic contractions, which were considered abnormal, are a normal response to a 50-Hz stimulus. Investigators have demonstrated that there is considerable variability in response patterns to repetitive stimuli.^{60–62} Some of the response variability may be attributable to whether stimulation is performed with constant current or constant voltage. Because tetanic responses are not considered now to be abnormal, the proportion of nerve rootlets divided has decreased (without a decrease in effectiveness), and the frequency of postoperative hypotonia has diminished.

Many neurosurgeons now perform lumbar dorsal rhizotomies without using neurophysiologic monitoring and base the percentage of dorsal roots to be divided on the preoperative clinical examination. Steinbok et al compared the outcomes of 22 patients who had lumbar dorsal rhizotomies without electrophysiologic guidance and the outcomes of 22 patients who had lumbar dorsal rhizotomies with electrophysiologic guidance, and they found no differences in spasticity reduction or any other parameters.⁶³ I used monitoring for perhaps 15 years, but for the past 7 years I have used no monitoring and have observed no difference in spasticity outcomes.

The critical aspect of SDR is not electrical stimulation, but rather patient selection. Good candidates for SDR are usually 5 to 8 years old with spastic diplegia that is inhibiting their gait; they have good strength in their legs, and mild contractures. Few children with CP meet these criteria. Functional decline in children undergoing SDR after age 10 has recently been reported.⁶⁴ Dorsal rhizotomies do not improve dystonia, although they are performed relatively often in children with unrecognized dystonia, nor do dorsal rhizotomies reliably improve spasticity in children with familial spastic paraparesis.

Children treated by Peacock's method have significantly decreased spasticity in the lower extremities, improved range of motion, and improved gait, with longer stride length and faster cadence. McLaughlin et al⁶⁵ performed a meta-analysis of data from three RCTs of SDR. Spasticity was significantly decreased, and function, as evaluated by the GMFM, was significantly improved. Although SDR has been reported to decrease the development of musculoskeletal deformities and contractures, more recent publications indicate that many children will require orthopedic operations.^{66,67}

Although some series report a regression of the GMFM to baseline values 10 years after SDR, most studies report persistent improvement in GMFM and GMFCS levels.^{66–68} Two of the best long-term evaluations of SDR, from Peacock's original group, found that 20 years after SDR, a prospective gait analysis in 13 patients showed improved locomotor function and

improvements in the GMFCS levels.^{69,70} Spasticity, stride length, and quality of gait may also improve after SDR in children with spastic hemiparesis.⁷¹

Cervical SPR has been performed to treat spasticity of the biceps and of the wrist and finger flexors, which results in contractures and poor hygiene.⁷² In my experience, cervical SDR improves spasticity in the upper extremities approximately as well as lumbar SPR improves spasticity in the lower extremities, but upper extremity function is less likely to improve. Cervical SDR is infrequently performed, mainly because of the availability of treatment alternatives such as IM injections, peripheral neurectomies, and orthopedic operations.

Peripheral Neurectomies

Peripheral neurectomies have been used in Europe and India more often than in the United States and are an underutilized operation. Like IM injections, they do not reduce spasticity per se but rather weaken contraction of the muscle. Thus, they are performed to treat focal spasticity rather than generalized spasticity. Spasticity in the plantar flexors, hip adductors, and elbow flexors is treated by peripheral neurectomies of the posterior tibial, obturator, and musculocutaneous nerves, respectively.⁷³ The procedure is performed to increase range of motion, facilitate care, and lessen the development of contractures, rarely with the goal of improving function. It is performed under general anesthesia and can be done either nonselectively, dividing 50 to 80% of the nerve, or selectively, with intraoperative stimulation of nerve fascicles to identify motor branches whose stimulation results in strong muscle contractions. Selective motor fasciculotomy for spastic upper extremities was reported for 20 patients whose mean age was 13 years.⁷⁴ Fasciculotomies of the musculocutaneous, median, and ulnar nerves reduced spasticity of the affected muscles and improved self-care.

Treatment Selection

Given the plethora of methods available to decrease spasticity, both those who treat and those who receive treatment may be perplexed. It is important to remember that not all spasticity needs to be treated, and that treatment goals should be carefully identified before any therapy is undertaken. The reasons for not needing to treat all patients with spasticity include the following: (1) Some mild spasticity causes no interference with function and no orthopedic problems. (2) Some spasticity is clinically useful in individuals with weak extremities, to augment contractions of weak muscles. (3) Spasticity that causes extremity stiffness may help maintain an erect posture of the neck and trunk; if it were treated, the arms and the legs might relax, but the child might then be unable to hold the head up or to sit upright.

In general, treatment goals include improving function, facilitating care, preventing or minimizing contractures, and, infrequently, reducing painful muscle spasms or cramps. The goal of improving function may include general goals such as easier ambulation, dressing, or transfers, but unfortunately, more specific goals such as improved handwriting or swallowing cannot be predicted. In my experience, upper extremity function improves in approximately 60% of children with spastic quadriplegia after ITB, and speech intelligibility and swallowing

improve in approximately 40%, but I know of no way to predict which children will have such improvement; screening trials do not answer the question.

Treatment selection also depends on the severity of the spasticity, the extent of involvement (focal or diffuse), and the child's age. Muscle tone with a score of 2 on the Ashworth Scale is mild and usually does not need to be treated; tone with a score of 3 to 5 usually does. Oral medications are of minimal, if any, help in treating severe spasticity. Focal spasticity is more appropriately treated with botulinum toxin injections than is diffuse spasticity.

Age is important for the following reasons: (1) Ablative procedures like SPR are usually delayed until the age of 4 to 5 years because brain maturation (and a decrease in spasticity) may occur by that time. (2) Children younger than 4 years are infrequently candidates for ITB pumps; their spasticity can usually be treated satisfactorily with oral medications and botulinum toxin. (3) SPR is infrequently performed in children older than 16 years if the goal is to improve function because their ability to strengthen weak muscles and to learn new gait patterns is more limited than that of younger children. Ablative procedures are more commonly performed in children for whom the treatment goal is to facilitate care rather than to improve function.

For children 1 to 4 years old with diffuse spasticity, treatment usually entails oral spasmolytics, which usually reduce Ashworth Scale scores from 3 or 4 down to 2. However, the score is infrequently reduced to normal, and infrequently to a degree such that the child no longer exhibits plantar flexion of the feet or scissoring (adduction) of the legs; botulinum toxin is often injected into those muscles to prevent contractures that might otherwise develop despite the oral medications.

The age at which SPR is performed varies according to the treatment goal: if improved ambulation is the goal, SPR is performed most commonly in children 5 to 8 years old but is infrequently performed after age 12. If the goal is to facilitate care and age is not an issue, the operation can be done at any time, preferably before contractures develop. If the goal is to facilitate the care of children with spastic quadriplegia (whose spasticity involves the lower extremities more than the upper), lumbar SPR is probably the best treatment—it is definitive and effective. Of children with spastic quadriplegia that involves the upper and lower extremities equally, those who are functional are probably best treated by ITB and those who are nonfunctional either by ITB or by combined cervical and lumbar dorsal rhizotomies.

ITB is useful in ambulatory children who have some leg weakness because doses can be increased slowly as muscle strength improves. ITB is probably not helpful in improving the ambulation of patients with spastic diplegia who are in their late teens or older because of their limited ability to improve their strength and learn new gait patterns, although it may improve trunk and upper extremity mobility and function in that age group. ITB is also appropriate for children with spastic paraparesis after spinal cord injuries. For those with *nonfamilial* spastic paraplegia, either SPR or ITB may be used; SPR is probably preferable because of its lower complication rate. Children with spastic quadriplegia after spinal cord injuries are usually treated with ITB.

Peripheral neurectomies may be considered in children with focal spasticity that has not yet caused substantial

contractures. The children have usually been given repeated botulinum toxin injections for 1 to 3 years but need therapy that is more permanent.

76.2 Dystonia

Dystonia has been defined as "... a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both."² Dystonia is classified according to the body regions involved: focal if one region (such as one upper extremity) is involved, segmental if adjacent regions (such as the neck and upper extremity) are involved, hemidystonia if one side of the body is affected, and generalized if the entire body is affected. Dystonia is also characterized as primary or secondary: primary if no underlying pathology can be identified and the individual shows no other neurologic abnormalities, and secondary if the dystonia can be attributed to a structural cause (such as a lesion of the basal ganglia). Some clinicians add a third category, hereditary. The term *primary dystonia* is synonymous with the previously used term, *dystonia musculorum deformans*. Whether primary or secondary, dystonia is characterized by simultaneous contractions of agonist and antagonist muscles, and to a considerably greater extent than occurs in spasticity.

Primary dystonias are diagnosed by genetic analysis. At present, 21 different abnormalities in the *DYT* (TORIA) gene have been identified, causing disorders such as early-onset primary dystonia (*DYT1*), X-linked dystonia-parkinsonism ("Lubag," *DYT3*), dopa-responsive dystonia (Segawa syndrome, *DYT5*), and myoclonic dystonia (*DYT11*). Secondary dystonias are diagnosed most often by abnormalities in the basal ganglia, particularly the putamen. Hereditary dystonias may be caused by Huntington disease, Wilson disease, neuroacanthocytosis, Rett syndrome, Leigh disease, and neurodegeneration associated with iron deposition (Hallervorden-Spatz disease, PKAN [pantothenate kinase-associated neurodegeneration] disease), and are diagnosed by tests specific for each of those disorders.

Pediatric neurosurgeons encounter dystonia frequently in children with CP, occasionally after head injury, stroke, or tumor removals; uncommonly in children with hereditary dystonias; and rarely in children with primary dystonia. CP usually causes generalized dystonia but occasionally hemidystonia or dystonic paraparesis, whereas stroke or head injuries are more likely to cause focal dystonia or hemidystonia and to follow an initial hemiplegia. In the series of Saint Hilaire et al,⁷⁵ no patient with CP had focal dystonia. Posttraumatic dystonia usually occurs after severe head injuries but may follow minor injuries, and in either case it may develop months to years after the injury and may worsen for a few years before stabilizing.⁷⁶ As a general rule, dystonia that develops several years after an injury or an ischemic event is less likely to be severely disabling than dystonia that begins soon afterward.

76.2.1 Epidemiology

Primary dystonia occurs most frequently in Ashkenazi Jews, affecting 1 per 3,000 to 1 per 9,000 in that population. In non-Jewish people, the incidence ranges between 1 per 10,000 and 1 per 30,000. Secondary dystonia is far more common, occurring in 15 to 25% of individuals with CP.

76.2.2 Clinical Presentation

Dystonia associated with CP may not be clinically evident until 3 to 15 years of age, perhaps because a certain degree of myelination is necessary before the dystonic movements can become apparent.⁷⁷⁻⁷⁹ Dystonic movement in CP may cause the extremities to writhe in random motions or to contract repeatedly in abnormal postures. Dystonia may cause intermittent deviation of the head to one side, posterior arching of the neck and trunk, and intermittent extension or adduction of the upper and lower extremities. The movements are not stereotypic, as are the abnormal postures seen in infancy (e.g., the asymmetric tonic neck reflex). Dystonia is increased by excitement and ceases with sleep. Dystonic children are typically thin because of the calories expended during sustained muscle contractions, and they have muscles that are well developed because of repeated isotonic contractions. Although the brain lesions in CP are static, the dystonic movements may worsen over several years.

Primary dystonia in children is graded most frequently with the Burke-Fahn-Marsden (BFM) Dystonia Rating Scale, which was developed to grade primary dystonia in adults.⁸⁰ Secondary dystonia is graded with either the Barry-Albright Dystonic (BAD) Scale, which was developed and validated for use in children with secondary dystonia, or with the BFM Scale.⁸¹

Dopa-responsive dystonia (Segawa disease) may be misdiagnosed as dystonic CP.⁸² Dopa-responsive dystonia begins during childhood, often with gait difficulties or as dystonia in a foot. It has diurnal variations in 75% of cases and frequently a positive family history, and it may be associated with spasticity or Parkinsonian features. Dopa-responsive dystonia responds dramatically and chronically to low doses of levodopa, without the dyskinesia that occurs in adults treated with levodopa.⁸³ A trial of levodopa should be considered in children with dystonia unless they have an unequivocal historical and radiographic features of CP.

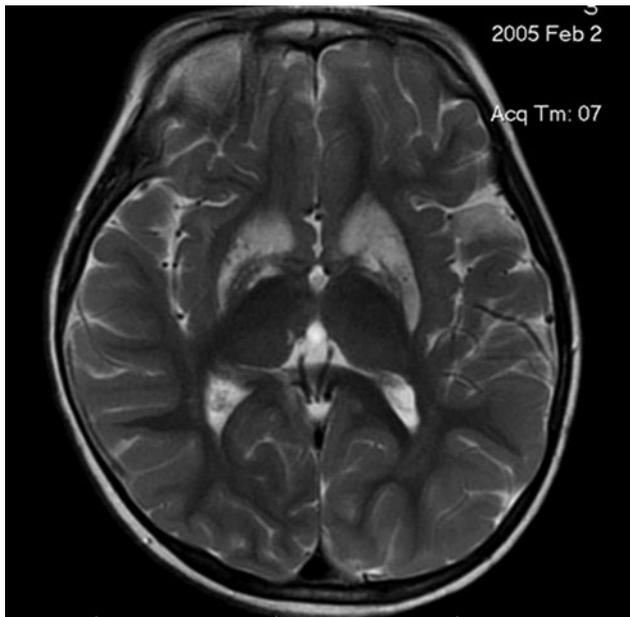


Fig. 76.2 Axial magnetic resonance image demonstrating caudate and putaminal changes associated with generalized secondary dystonia.

76.2.3 Pathology and Pathophysiology

There is no demonstrable pathology in primary dystonia. Secondary dystonias and some hereditary dystonias are associated with lesions in the basal ganglia, particularly in the caudate and putamen (► Fig. 76.2 and ► Fig. 76.3).

Cortical motor excitability appears to be increased in dystonia.⁸⁴ Positron emission tomography (PET) in adults with primary dystonia demonstrates overactive prefrontal and underactive motor cortical areas, consistent with inappropriate overactivity of the striatofrontal projections and underactivity of the primary motor areas.^{15,85} Recent experimental and clinical studies have shown reduced spontaneous activity in both the internal and external segments of the globus pallidus, with bursts and pauses, and reduced output from the internal globus pallidus, which may increase thalamic and cortical activity.⁸⁶

76.2.4 Treatment

Oral Medications

In general, oral medications are mildly to moderately helpful in treating both primary and secondary dystonia, and they are more helpful in younger children than older ones. ► Table 76.4 lists the commonly used agents. In treating secondary dystonia in children, baclofen (Lioresal) and trihexyphenidyl (Artane; Lederle Pharmaceuticals, Carolina, PR) are the first two drugs of choice.^{87,88}

Intramuscular Medications

Although botulinum toxin has not been approved by the FDA for use in children with dystonia, it has been approved for use in adults with focal dystonia (torticollis, blepharospasm) and is being used to treat many children with dystonia, both in clinical

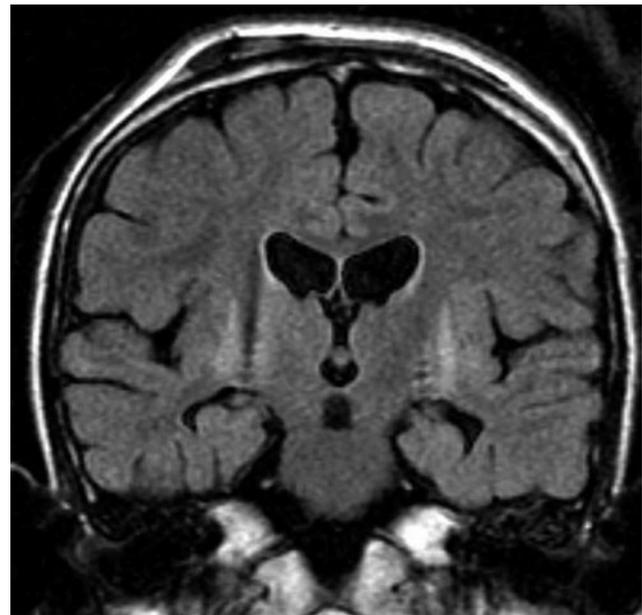


Fig. 76.3 Bilateral deep brain stimulation electrodes implanted into the internal globus pallidus to treat an adolescent with generalized dystonia.

Table 76.4 Oral medications for dystonia

Medication	Mechanism of action	Half-life (h)	Initial dosage	Maintenance	Side effects
Baclofen (Lioresal)	GABA _B agonist	3–4	2.5–10 mg/d	20–90 mg/d divided into 3 doses	Drowsiness, ataxia, confusion
Diazepam (Valium)	Benzodiazepine receptor agonist	36	0.1–0.2 mg/kg/d	0.1–0.8 mg/kg/d divided into 3 doses	Lethargy, tolerance
Dantrolene (Dantrium)	Impedes muscle contractility	3–9	0.5–1 mg/kg/d	12 mg/kg/d divided into 4 doses	Weakness, diarrhea, rash
Tizanidine (Zanaflex)	α ₂ -Adrenergic agent	2–3	4–8 mg/d	8–24 mg/d divided into 4 doses	Sedative, dizziness, hypotension

Abbreviations: GABA_B, γ-aminobutyric acid B-receptor.

research protocols and off label. Although botulinum toxin has been beneficial in treating adults with focal dystonias, such as torticollis and limb dystonias,^{89,90} its usefulness in children is somewhat limited to those with hemidystonia, in which injections into the affected muscles may not only decrease the dystonic movements but also improve hand and arm function and foot posture. Doses used for dystonic extremities are restricted by body weight; doses of 10 to 20 U/kg are commonly given.

Intrathecal Medication

In 1992, Narayan et al⁹¹ reported the first use of ITB for dystonia, in an 18-year-old with axial dystonia after a cerebral injury at birth. Baclofen is the only intrathecal medication that has been reported to improve dystonia. Its site of action in doing so is unknown. Several clinical features suggest an intracranial (cortical) site of action, with inhibition of the excessively stimulated premotor and supplementary motor cortex.⁹² However, Dachy and Dan⁹³ found motor evoked potentials to be preserved and the H-reflex to be inhibited after ITB, observations that are more consistent with a spinal site of action.

Penn et al⁹⁴ treated 10 adults with various motor disorders and observed improvement in those with focal dystonias. We have used ITB to treat generalized dystonia in more than 300 children during the past 15 years, primarily children with secondary dystonia and a few with hereditary degenerative dystonia. We have found that dystonia is significantly improved in 85 to 90%, ease of care and comfort are improved in 85%, and speech and function are improved in one-third.⁹² We observed several differences compared with the use of ITB in spasticity. First, dystonia often does not respond to bolus screening doses, so if screening is to be done, a continuous infusion via an intrathecal catheter connected to an external microinfusion pump is appropriate. Second, the doses to which dystonia responds are higher than those used for spasticity; dystonia usually responds to doses of 400 to 600 μg/d, although doses of 1,000 μg/d or higher may be needed. These high doses are not associated with lethargy or other CNS side effects. The response rate of children with generalized secondary dystonia to ITB is similar to the response rate of children with spasticity. Because of that, we now usually do not screen response to ITB before implanting a pump for dystonia. However, if a child has a combined movement disorder (e.g., a mixture of dystonia, chorea, and athetosis), an infusion trial to evaluate the response is indicated.

Although children with spasticity retain their responsiveness to ITB for many years, it appears that perhaps 10% of children

with dystonia lose their responsiveness to chronic ITB infusion during the first 1 to 2 years of therapy. Overall, however, ITB offers far better treatment of severe secondary generalized dystonia than any oral medication, and probably better than any currently available operation. Children with dystonia associated with glutaric aciduria also respond to ITB, although not as well as children with secondary dystonia; they do not seem to respond to deep brain stimulation. Children with generalized dystonia have significant improvement in dystonia in all body regions after continuous ITB. Experience with ITB for primary dystonia is limited, but thus far, ITB appears to bring about no significant improvement.

Since the publication of the second edition of this text, ITB infusions in children with secondary dystonia have been reported to significantly improve both upper limb function and dystonia, and to improve individually identified functional goals, caregiver burden, and pain.^{95–97} In addition, baclofen infusion has been extended to the intraventricular route, which appears to achieve a reduction in dystonia similar to that seen with the intrathecal route, to have a similar complication rate, and to cause fewer catheter complications.^{98–100}

Stereotactic Procedures

Because dystonia in children often worsens for a few years before stabilizing, permanent and nonadjustable procedures such as thalamotomies are usually deferred until dyskinesia has stabilized. Because of this, there are few published reports describing the results of thalamotomies for children with hyperkinetic movement disorders.^{101,102} Speelman and van Manen¹⁰³ reported that 8 of 18 patients who had CP treated with stereotactic thalamotomies showed improvement at a mean of 21 years after operation. Posttraumatic dystonia is often temporarily improved by stereotactic thalamotomies, but the dystonia may worsen later. Pallidotomies are being tried, but outcome data in children are sparse. Pallidotomy has been reported to improve dystonia in a child with Huntington disease.¹⁰⁴ In primary dystonia, 60 to 80% improvements in the BFM Dystonia Scale have been reported after pallidotomy.

Deep brain stimulation (DBS) is a potential treatment for children and adolescents with severe dystonia that is unresponsive to oral medications. DBS appears to act like a lesion, interrupting the abnormal cortical–basal ganglia–cortical loop that generates the dystonic movements. For children with primary dystonia, DBS is the preferred treatment after oral medications; for those with secondary dystonia, ITB is probably the best

treatment after oral medications, with DBS reserved for those who do not respond to ITB.

Coubes et al¹⁰⁵ published the first substantial series of dystonic children treated with DBS. They reported that in 25 children with primary dystonia, BFM Dystonia Scale scores improved by 80 to 84%, and that the improvements persisted for 2 years or longer. In 10 children with secondary dystonia, the BFM Dystonia Scale scores improved by 31%.¹⁰⁵ Air et al recently reported their results of DBS for various types of dystonia; in 13 children with primary dystonia, the BFM Dystonia Scale scores improved by 75%, but in 18 children with secondary or heredo-degenerative dystonia, the scores improved by only 10 to 20%.¹⁰⁶ Haridas et al treated 22 children with primary generalized dystonia for 1 to 3 years with DBS and found that motor subscores improved by 84%, 93%, and 94% at 1, 2, and 3 years, respectively, with equivalent improvements in function.^{10,7} Although most reports of DBS for secondary dystonia have not been encouraging, a recent report of 14 children with dystonic CP who were treated with DBS in a noncontrolled, nonblinded manner reported significant reductions of dystonia on two dystonia scales and improvements in the BFM Dystonia Disability Scale.¹⁰⁸

For children with severe, refractory, secondary or heredo-degenerative dystonia who do not respond to oral medications and for whom ITB and DBS are not available, myotomies, cervical rhizotomies, and selective peripheral denervation may be helpful.¹⁰⁹

Patients with focal upper extremity dystonia are being treated with motor cortical stimulation, in which an epidural electrode strip or grid is implanted over the motor cortex innervating the dystonic region (► Fig. 76.4).^{110–113} The rationale for motor cortical stimulation is similar to that for DBS—interruption of the pathophysiologic cortical–basal ganglia–cortical circuit. There are no published reports of motor cortical stimulation in children. We used it in two young adults with focal secondary dystonia and observed mild improvement in dystonia, but no change in function.

76.3 Athetosis and Chorea

Athetosis is characterized by slow, distal, wormlike, writhing movements of the extremities, often with fanning and hyperextension of the digits. It may be unilateral or bilateral. The term also applies to the writhing perioral movements that garble the speech of individuals with athetoid CP. The pathophysiology of athetosis is unknown. It affects perhaps 10% of individuals with CP (far fewer than before kernicterus could be treated effectively), occurs more often in those born at term, and is more often associated with normal intellect. Athetosis begins during the first 2 years of life in 65% of cases and before the fifth year in 92%.¹¹⁴ It is nonprogressive and becomes associated later in childhood with other CP movement disorders in approximately 45% of cases.¹¹⁵ Athetosis is often confused with dystonia. Some movement disorder specialists consider athetosis to be a form of dystonia, but the two are different. Dystonia responds to ITB well, and athetosis responds only mildly. Choreoathetosis can be graded on a dyskinesia impairment scale.¹¹⁶

The classic pathologic substrate in athetoid CP is status marmoratus of the corpus striatum—which is marbling caused by a

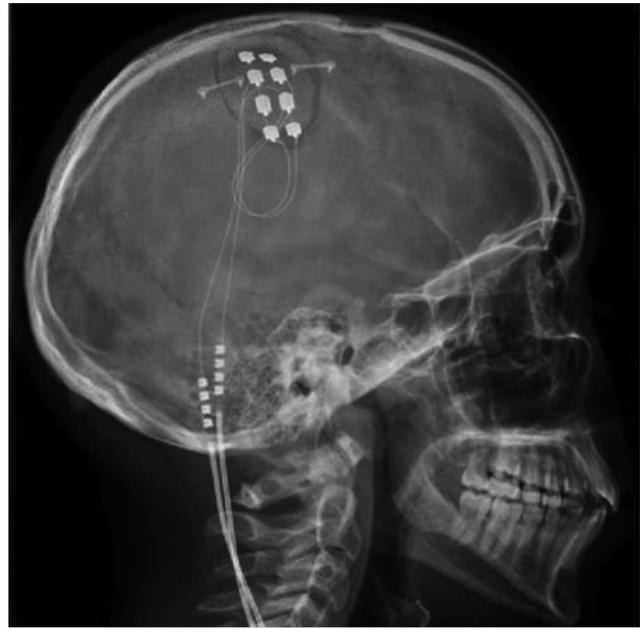


Fig. 76.4 Epidural cortical motor stimulation via a strip electrodes for focal dystonia of an upper extremity.

coarse network of myelinated fibers that disturb the normal radial pattern. Athetosis after kernicterus is typically associated with lesions in the globus pallidus and subthalamic nucleus; athetosis after head injury is more often associated with lesions in the striatum. MR imaging of children with athetoid CP shows no abnormalities in 40%. It shows hyperintense lesions in the ventrolateral thalamus in 60% and in the putamen in 30%.¹¹⁷

Severe athetosis is exceedingly difficult to treat. No oral medications are particularly effective, botulinum toxin injections are unhelpful, ITB helps only mildly, and most case reports of DBS for athetosis indicate little benefit.

Chorea has been described as “a state of excessive, spontaneous movements, irregularly timed, nonrepetitive, abrupt in character” and is characterized by involuntary, rapid, brief, unsustained, dancelike movements.¹¹⁸ Chorea is often worse at rest than during movement. Chorea has been reported to develop in up to 25% of patients with CP, often between 3 to 5 years of age, and is usually associated with an IQ of at least 70.¹¹⁹ Recently, however, the frequency of chorea in CP has appeared to be lower, probably 5 to 10%. Choreiform CP must be distinguished from benign hereditary chorea, which may also commence in early childhood but is not associated with other hallmarks of CP.¹²⁰ Chorea may progress for several years during childhood, perhaps because of the maturing anatomical substrate required for these movements. The pathophysiology of chorea is poorly understood but is thought to involve either destruction or inhibition of the subthalamic nucleus.²

Chorea is treated with tetrabenazine, benzodiazepines, propranolol, and haloperidol. Tetrabenazine, a dopamine receptor blocker, has been reported to be quite effective for chorea.¹²¹ Benzodiazepines, particularly clonazepam, are sometimes effective, although tolerance may develop (► Table 76.5).

In the past 5 years, we have used ITB to treat a few children with severe generalized chorea and observed little improve-

Table 76.5 Oral medications for hyperkinetic movement disorders

Medication	Mechanism of action	Oral doses	Movements treated	Side effects
Trihexyphenidyl (Artane; Lederle Pharmaceuticals, Carolina, NC)	Anticholinergic	2–15 mg divided into 2 doses	Dystonia	Dry mouth, nausea, blurred vision
Diazepam (Valium; Roche, Nutley, NJ)	Benzodiazepine receptor agonist	1–10 mg divided into 2 or 3 doses	Athetosis	Drowsiness, ataxia
Baclofen (Lioresal; Novartis Pharmaceuticals, East Hanover, NJ)	GABA agonist	20–120 mg divided into 2 or 3 doses	Dystonia	Lethargy, nausea, hypotonia
Carbamazepine (Tegretol; Novartis Pharmaceuticals)	Affects sodium channels	15–20 mg/kg/d divided into 2 or 3 doses	Dystonia	Drowsiness, rash, bone marrow suppression
Clonazepam (Klonopin; Genentech, South San Francisco, CA)	Benzodiazepine receptor agonist	0.1–0.2 mg/kg/d divided into 2 or 3 doses	Chorea, athetosis	Behavior problems, blood dyscrasias, tiredness, extrapyramidal reactions
Levodopa/carbidopa (Sinemet; Bristol-Meyers Squibb, New York, NY)	Indirect dopamine receptor agonist	1–2 tablets 2 or 3 times daily	Dystonia	Nausea, chorea
Propranolol (Inderal; Akrimax, Cranford, NJ)	Blocks β -adrenergic receptors	40–120 mg/d divided into 2 or 4 doses	Chorea, tremor	Bradycardia, dizziness, depression, bronchospasm
Haloperidol (Haldol; Janssen Pharmaceuticals, Titusville, NJ)	Dopamine receptor antagonist	0.5–3 mg/d divided into 2 or 3 doses	Chorea	Sedation, extrapyramidal reactions

Abbreviations: GABA, γ -aminobutyric acid.

ment. Radio-frequency lesions have been made in the ventrolateral thalamus and ventroposterior pallidum to treat chorea that is unresponsive to medications. DBS may have a role in the treatment of unilateral choreiform CP, but experience is limited.¹²²

The potential of DBS to help patients with mixed movement disorders, such as combined dystonia and choreoathetosis, was demonstrated in a recent multicenter study of 13 adults with dystonia–choreoathetosis who had only mild abnormalities of the basal ganglia on MR imaging.¹²³ Their BFM Dystonia Scale scores improved from a mean of 44 preoperatively to 35 at 1 year postoperatively. Function, pain, and mental health–related quality of life were significantly improved. Such results suggest trials of DBS in children with similar mixed movement disorders if their MR imaging findings are relatively normal.

Pearls

- IM botulinum toxin injections decrease spasticity in localized muscles and act as a bridge to treat spasticity in children between 3 and 6 years of age, after which patients are old enough for more definitive procedures.
- ITB improves spasticity in the upper and lower extremities and is often associated with improved activities of daily living and improved communication.
- Lumbar dorsal rhizotomies provide permanent relief of spasticity, improve spasticity in both the upper and lower extremities, and often improve gait, with results persisting as long as 20 years.
- Generalized secondary dystonia is frequently misdiagnosed as spasticity, is common in children with CP, and can be treated effectively with ITB.
- DBS is highly effective for primary dystonia, mildly to moderately effective for secondary dystonia, and helpful for some individuals with mixed dystonia–choreoathetosis.

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77 Shunt Infections

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Hydrocephalus is the most common neurosurgical disorder managed by pediatric neurosurgeons and perhaps the one associated with greatest morbidity. In the United States alone, it has been estimated that there are between 38,200 and 39,900 admissions per year for pediatric hydrocephalus, accounting for more than 400,000 hospital days and costing between 1.4 billion and 2.0 billion dollars.¹ Although in recent years there has been a resurgence of interest in alternative methods of treatment of hydrocephalus, including endoscopic third ventriculotomy and choroid plexus ablation, shunt devices continue to be the mainstay of hydrocephalus treatment. The complications and morbidity associated with the placement and maintenance of ventricular shunts are well documented in the neurosurgical literature, and in virtually all series the problem of shunt infection has been a significant feature. Although infection rates as low as 1.04% have been reported,² rates between 3 and 15% are more representative of neurosurgical practice.^{3–9} Among children with shunt infection, a mortality rate of 10% has been reported¹⁰ furthermore, seizure disorders,¹¹ cognitive impairment, and reduced academic achievement^{10,12} are more common in these children than in those who have not had infection. In addition to the clinical consequences of shunt infection, there is an economic burden, given that it is estimated that the hospital cost of treating a shunt infection is \$50,000, making it the most costly implant-related infection in the United States.¹³

Although neurosurgeons have long recognized the importance of reducing shunt infection rates and numerous preventative strategies have been employed in pursuit of this goal, the strategies are institution-based, variably applied, and frequently unsupported by clinical evidence.¹⁴ Even in more recent series, between 4 and 12% of shunts become infected within 6 months of placement.^{15,16} In this chapter, the etiology of shunt infections is examined, and the contemporary understanding of the microbiology and pathogenesis of shunt infection is reviewed. Surgical management of shunt infection is discussed, and guidelines aimed at preventing or reducing shunt infection and its sequelae are presented.

77.1 Etiology and Pathogenesis

Infection results when a shunt becomes contaminated by an organism capable of establishing growth at the operative site, within the cerebrospinal fluid (CSF) and/or on the shunt hardware itself. Contamination may occur (1) at the time of shunt insertion because of contamination of the shunt tubing, CSF, or exposed wound; (2) through the wound during the early post-operative period before full skin integrity is re-established; or (3) after insertion by direct contamination (e.g., following shunt tap or by contiguous spread of abdominal infection).

An etiologic distinction is made between infections that begin as surgical wound infections enhanced by the presence of a biomaterial (external infections) and those that begin with colonization of the shunt itself (internal infections).¹⁷ From a clinical perspective, infections may be classified according to their location as superficial incisional, deep incisional (below

the fascia, with or without extension to the external part of the shunt), or CSF (infection within the shunt, ventricle, or peritoneum). Unless stated otherwise, we have used the term *shunt infection* to indicate infection of the CSF.

77.2 Causative Bacteria

The majority of shunt infections are caused by staphylococci (gram-positive cocci). Staphylococci are divided into two groups on the basis of their ability to produce the enzyme coagulase and are easily differentiated in the laboratory by the coagulase (or other equivalent) test. *Staphylococcus aureus* produces coagulase and is therefore coagulase-positive. Most staphylococci do not produce coagulase, and these comprise the coagulase-negative staphylococci (CoNS). Where the CoNS have been accurately identified in human infection, *Staphylococcus epidermidis* is the most commonly found species. In almost all reported studies of shunt infection, CoNS are the most common infecting agents, accounting for at least half of cases. *S. aureus* accounts for a further quarter of cases.^{18–23} The remaining quarter of cases are due to gram-positive rods, other gram-positive cocci, and gram-negative rods (► Table 77.1). Propionibacteria are a not uncommon cause of shunt infection; however, the organisms can be difficult to isolate, and prolonged anaerobic culture is recommended.²⁴

The microbiological profile of shunt infections that present a year or more after shunt insertion is different. In these “late” infections, staphylococci are seen less often, and there is a predominance of gram-negative organisms. These infections are less likely to be related to the shunt insertion procedure (hence the lower preponderance of *Staphylococcus* species), and in as many as three-quarters of cases some additional event, such as peritonitis, hematogenous spread, or bowel perforation, can be identified as the precipitating factor.²⁵

77.2.1 Source of Infecting Bacteria

It is clear that the majority of shunt infections are caused by gram-positive pathogens that are typical of the commensal skin flora, and an association has been demonstrated between perioperative skin bacterial density and the risk for shunt

Table 77.1 Organisms responsible for shunt infection

Organism	Shunt infections (%)
Coagulase negative <i>Staphylococcus</i>	60
<i>Staphylococcus aureus</i>	18
Gram positive rods (<i>C. diphtheriae</i> , <i>P. acnes</i>)	10
Other gram positive cocci (<i>Streptococcus</i> , <i>Micrococcus</i> , <i>Enterococcus</i>)	6
Gram negative rods (<i>E.coli</i> , <i>Pseudomonas</i> , <i>Enterobacter</i>)	6

Data from references Kanev et al.^{1–10}

infection.²² Skin preparation (even with alcohol-based agents, which are more effective than aqueous agents) will kill the majority of skin surface organisms. However, some bacteria in the deeper layers of the epidermis and in hair follicles may survive this process, and indeed, in two studies in which wound swabs were taken during shunt operations, positive cultures were obtained in 37% and 58% of cases, respectively.^{26,27} Whether or not the organisms cultured from operative swabs are exclusively from the patient (as opposed to the surgeon or operative environment), and whether it is these specific organisms that will be responsible for subsequent shunt infection, remain controversial.

Shunt contamination may theoretically occur through the deposition of airborne organisms on shunt components or the wound; however, there is little evidence to assess the contribution of this route, and its role is not thought to be significant. With respect to the surgeon as a source of pathogens, in one study cultures from the surgeon's gloves at the end of shunt surgery were positive for skin commensal bacteria in 39% of cases.²² In another study, breach of the surgeon's gloves was identified in one-third of cases, and this was an independent risk factor for shunt infection in that series.²⁸ Although the practices of double gloving, glove changing, and minimal shunt handling during surgery are supported by these findings, the evidence that commensal bacteria from the surgeon are an important source of shunt infection pathogens is weak. The patient's own flora continue to be the most commonly cited source of shunt-infecting pathogens, although again, supporting evidence is far from conclusive. Seven of nine shunt infections studied by Bayston and Lari were due to organisms that had been cultured preoperatively from the patient,²⁷ although whether the typing methods available at that time can be relied upon to establish that these were identical species might be debated. Shapiro et al found that only 20% of shunt infections could be related to cultures from the skin incision,²³ and in a prospective study, Pople et al identified shunt infections in 3 of 30 infants younger than 6 months, although in only one of these were the authors confident that the organism originated in the patient's flora.²² In the authors' experience, intraoperative contamination has been clearly demonstrated; however, we were unable to show a clear association between intraoperative bacterial isolates and the organisms responsible for subsequent shunt infection.²⁶ These apparently disparate findings might be explained by the suggestion that the surgical wound is contaminated by multiple strains of skin bacteria yet only a limited number progress to infection. Furthermore, in the days following surgery, as the commensal flora repopulates, the sutured surgical incision likely remains a potential portal of entry for bacteria.

77.2.2 Bacterial Factors

The mechanisms by which bacteria infect shunts have direct implications not only for our understanding of the treatment of shunt infection but also for the development of preventative strategies. Soon after placement of a shunt, there is a local tissue response that results in the deposition of host proteins over the tubing. Certain bacteria have surface-binding proteins or adhesins capable of binding directly to the shunt surface or to host proteins, thus facilitating bacterial adhesion to the

catheter; this represents the first step toward shunt infection. It is now known that once bacterial adhesion has taken place, genetically driven metabolic changes occur within the bacteria. The bacteria become capable of producing an extracellular "mucoid" material rich in polysaccharides, glycolipids, and glycoproteins commonly referred to as "bacterial slime," although now more properly referred to as polysaccharide intercellular adhesin or exopolymer.²⁹ Colonies of bacterial cells are suspended within this exopolymer, and the resulting amalgam of cells and extracellular material, known as a biofilm, progressively coats the surface of the shunt tubing. The biofilm is a complex microenvironment in which there is an interaction between the infecting organism and the inflammatory host response. Additionally cell to cell signaling between bacterial cells results in expression of genes that further enhance their ability to produce exopolymer.^{29,30} The high failure rate of antibiotic therapy alone as a treatment for shunt infection has been attributed to the effect of the biofilm, which constitutes a physical barrier to the penetration of antibiotics. The reality is likely to be a far more sophisticated developmental strategy on the part of the bacteria. It is now known that early on in the establishment of the biofilm, additional phenotypic changes take place within the bacteria that modify some of the pathways that would previously have been targeted by the antimicrobials, thus further ensuring survival and propagation of the biofilm.³¹ This is important when treatment strategies are considered because organisms in an established biofilm are unlikely to be eradicated by antibiotics alone; hence the need to remove the shunt as part of the shunt infection treatment strategy.

These preliminary stages of shunt infection—initial bacterial adhesion and early proliferation of bacteria within the biofilm—represent potential targets for preventative strategies, and the recent generation of hydrogel-coated and silver- or antibiotic-impregnated shunts has been developed with this in mind.

Interestingly, the introduction of antimicrobial-impregnated shunts may have changed the demographic of shunt infection, with an apparent reduction in the incidence of CoNS shunt infections (► Table 77.2).

S. aureus organisms are additionally more likely to be responsible for incisional infections with or without involvement

Table 77.2 Comparison of organisms responsible for shunt infection before and after the introduction of Bactiseal catheters

Organism	Historical cohort (1993–2003) 1592 shunts Infections = 133 (8.35%)	Bactiseal cohort 2003–2010 499 shunts Infections = 25 (5.10%)
Coagulase negative staphylococci	69	4
<i>Staphylococcus aureus</i>	42	10
Propionibacteria	2	4
Streptococcal/enterococcal sp.	10	5
Gram negative	5	2
Organism not isolated	7	1

Data from Departments of Neurosurgery and Microbiology, Great Ormond Street Hospital for Children, London, UK.

of the adjacent shunt because they produce a range of toxins and enzymes that allow them to survive the host cellular immune response. Therefore, *S. aureus* is more often responsible for those infections that begin with wound-related problems, such as wound breakdown, stitch abscess, and CSF leakage.

77.3 Timing of Shunt Infection

Shunt infection develops at a median time of 3 weeks (interquartile range, 1.5 to 5 weeks) after shunt surgery.³² Approximately 70% of shunt infections present within 2 months of shunt surgery, and 80% have presented by 6 months.³³ This temporal association supports the assertion that shunt infection is essentially a surgical complication that many would argue is potentially avoidable by appropriate attention to surgical technique.² The bacterial pathogenesis of acute shunt infection is discussed above. Shunt infections occurring 1 year or more after surgery are considered late infections and comprise up to 12% of cases.¹⁰ Both the causative bacteria and the underlying mechanism of shunt infection tend to be different. Two mechanisms of late shunt infection are to be considered. In the first mechanism, infection is likely initiated at the time of shunt insertion but is slow to manifest. Particularly indolent shunt infections, such as those caused by *Propionibacterium acnes*, typify this mode of infection. The causative organism may have been inoculated into the peritoneum at the time of surgery yet proliferates slowly, resulting in pseudocyst formation or less frequently ascites.³⁴ The presentation in such cases reflects poor CSF absorption, causing abdominal distension or impaired distal drainage. The second mechanism of late shunt infection is due to a post-insertion event, such as appendicitis, erosion of the catheter into the colon, or abdominal surgery. An underlying cause is present in as many as three-quarters of cases, and although the source may not be immediately evident, an exhaustive search should be pursued. Less obvious candidates include hematogenous spread from distal sites, such as the ear, nose, throat, urinary tract, and lungs.^{25,35} Late infections can occur many years after shunt surgery, and it has been suggested that the risk for such late shunt infection is cumulative over time.²⁵

77.4 Risk Factors for Shunt Infection

Numerous studies have sought to identify risk factors for the development of shunt infection; however, in many single-institution studies, the validity of the findings is compromised by small sample size and additional confounding factors, such as patient selection bias, variations in operative technique, and antibiotic prophylaxis. Inclusion criteria frequently differ between studies; some include only primary insertions, whereas others include revisions, and many studies relate to particular age groups or etiologies of hydrocephalus. Furthermore, some authors report infection rates per procedure rather than per patient, and as a result patient-related risk factors can be easily overlooked. During the following review of risk factors, it is important to take these issues into account because they may shed light on the apparently contradictory findings of some studies.

Pediatric patients with hydrocephalus are an extremely heterogeneous population, and although the following factors are among those that have been repeatedly identified to increase the risk for shunt infection, the risk to an individual patient will commonly reflect a complex interplay of more than one of these elements. Broadly speaking, one can usefully distinguish between risk factors that are intrinsic to the patient (or the patient's underlying condition) and those that are extrinsic.

77.4.1 Intrinsic Factors

Age

Most studies concur that the risk for shunt infection is greater in children than in adults.^{36,37} Even after other variables have been accounted for, young age appears to be an independent risk factor for shunt infection.^{10,32} It is within the infant population that the effect of age is most marked. Kulkarni et al found that premature infants with a gestational age of less than 40 weeks at the time of surgery were at greater risk for shunt infection compared with older infants and children (hazard ratio [HR], 4.72; 95% confidence interval [CI], 1.71 to 13.06).²⁸ In the study of McGirt et al, placement of a ventriculoperitoneal shunt in a premature neonate was associated with an almost fivefold increase in the risk for shunt infection ($p < 0.1$).³⁸ Immunologic immaturity, greater density of the skin bacterial flora, and poor skin quality are among the reasons cited for the greater vulnerability of this group.^{22,39}

Etiology of Hydrocephalus

The intraventricular hemorrhage of prematurity accounts for a significant proportion of cases of pediatric hydrocephalus, and recent studies continue to demonstrate that infection rates and early revision rates are particularly high in this group.^{15,40,41} All shunt-related complications tend to be particularly prevalent in patients with myelomeningocele compared with other etiologies, and shunt infection is no exception. Shunt infection rates as high as 25% are reported even in large centers^{10,42} for this group of patients. Because patients in this group have particularly high rates of shunt revision surgery, the "per patient" risk for shunt infection is also high. This propensity for shunt infection is most likely related to the need for an additional transdural neurosurgical procedure (i.e., closure of the neural tube defect) because the risk for shunt infection tends to decrease in subsequent shunt procedures. Shunt placement before closure of the myelomeningocele, a high level of the myelomeningocele, and a very large size of the ventricles (Evans index > 70) have all been correlated with increased shunt infection rates.^{43,44} When feasible, shunt placement is best deferred until after the myelomeningocele closure, and even then only after a critical appraisal of the need for shunt placement.⁴⁵

Number of Previous Shunt Procedures

Even after controlling for other factors, Simon et al showed that the risk for shunt infection following revision surgery was significantly greater than the risk at the time of initial shunt placement (HR, 3.0; 95% CI, 1.9 to 4.7), and that the risk increased as the number of revisions increased (HR, 6.5; 95% CI, 3.6 to

11.4).³² A prior history of shunt infection also increased the odds of subsequent shunt infection.^{38,46,47} The risk factors for repeated infection are not well understood at present, although the risk is highest in the 6-month period following initial shunt infection, and it is important to distinguish between relapse of an inadequately treated initial infection and a new infection in the same patient.

Other Intrinsic Factors

Other intrinsic factors that have been reported to increase the risk for shunt infection include low birth weight,^{39,48} and comorbidities, such as chronic respiratory disease and sepsis.¹⁸

77.4.2 Extrinsic Factors

Perhaps of more practical relevance are those risk factors that are extrinsic to the patient and diagnosis because these variables, in theory at least, are amenable to modification in an attempt to reduce shunt infection rates.

Cerebrospinal Fluid Leakage and Wound Infection

CSF leakage and wound infection are inextricably linked. CSF leakage through the surgical wound provides a conduit by which bacteria can enter and infect the shunt; moreover, wound infection compromises the integrity of the closure, thus facilitating CSF leakage. Both these surgical complications have consistently been shown to result in increased rates of shunt infection. In the prospective study of risk factors for shunt infection conducted by Kulkarni et al, a postoperative CSF leak was the strongest risk factor (HR, 19.16; 95% CI, 6.96 to 52.91),²⁸ a finding reinforced in a more recent prospective study, in which the incidence of shunt infection was 57.1% in patients with a CSF leak compared with 4.7% in those with no leak.⁴⁹ The importance of meticulous wound closure and diligent wound care in the postoperative period cannot be overemphasized.

Surgeon Experience

The influence of surgical experience on shunt infection rates has been specifically addressed in a number of studies, and most conclude that more experienced surgeons tend to have lower rates of shunt infection.^{18,33,50,51} However, surgical grade does not necessarily correlate with shunt infection rates,⁴⁹ and operative numbers are perhaps a more relevant index. In a study of more than 12,000 shunt procedures performed by 254 surgeons, Cochrane and Kestle observed an infection rate of 7% for surgeons whose shunt procedure numbers were above the 50th percentile and of 9.4% for those whose numbers were below the 50th percentile.⁵¹

Operative Factors

Numerous studies have sought to demonstrate a relationship between various operative factors and the development of shunt infection. These include, among others, an increased risk associated with hair shaving,⁵ intraoperative use of the endoscope,³⁸ excessive numbers of personnel in the operating

room,⁵² position of the case in the operating schedule,² and increased duration of surgery.^{20,52} Many of these studies, however, are retrospective single-institution audits and insufficiently powered; thus, the correlations identified may not be causative. One prospective study did identify repeated exposure of the shunt hardware to breached surgical gloves as a significant risk factor.²⁸

Although the role of airborne pathogens in the etiology of shunt infection remains unproven, the use of high-efficiency particulate air (HEPA) filters in the operating environment has been suggested. This has previously been advocated for orthopedic joint implant procedures, although a recent meta-analysis has questioned its role.⁵³ Currently, there is no evidence available on the effects of unidirectional HEPA-filtered laminar air flow and total-body exhaust suits in shunt insertion surgery.

77.5 Clinical Presentation

Shunt infection is almost always secondary to a surgical intervention. In a retrospective study of almost 1,000 patients with shunts younger than 21 years, factors associated with shunt infection were shunt surgery within the preceding 90 days (adjusted odds ratio [OR], 2.4; 95% CI, 1.3 to 4.4) and presentation with fever (adjusted OR, 8.4; 95% CI, 4.3 to 16.3).⁵⁴ Although shunt infection should always be considered when a child presents unwell or with unexplained symptoms, particularly fever soon after shunt surgery, a full history and clinical examination should be performed in all cases, with the examiner remaining alert to alternative diagnoses, such as upper respiratory tract infection, otitis media, and urinary tract infection (particularly in patients with myelomeningocele). Nonspecific symptoms of headache, vomiting, and lethargy will be present in half of children with shunt infection; thus, there is significant overlap with the symptoms of shunt blockage, and indeed shunt blockage may coexist with shunt infection. Additional clinical features, such as pyrexia and meningism, will increase the index of suspicion of shunt sepsis. Problems of surgical wound healing should be specifically looked for, in particular erythema along the shunt track, wound breakdown, purulent discharge, and CSF leakage, because these are strongly associated with shunt infection.⁴⁹

Less commonly, the presenting symptoms of shunt infection are related to the distal site of drainage. With ventriculoperitoneal shunts, abdominal pain, nausea, and swelling commonly herald a distal shunt infection. This presentation may occur many months after the shunt procedure (which is an exception to the usual temporal association between surgery and infection), and this likely reflects the low pathogenicity of the infecting organisms. Abdominal swelling may be caused either by the formation of loculi of infected CSF within the peritoneum or by the accumulation of infected ascites throughout the peritoneal cavity (► Fig. 77.1a).³⁴

Abdominal ultrasound can usually identify the septa or pseudocyst walls that typify compartmentalized collections of infected CSF and distinguish these from the diffuse free peritoneal fluid of infected ascites. The distinction may have implications for the future options for CSF drainage once the infection has been eradicated. In the case of a loculate infection, simply relocating the peritoneal catheter to a new abdominal site will



Fig. 77.1 (a) Abdominal swelling due to accumulation of infected CSF. (b) Protrusion of distal tubing through the mouth due to erosion of shunt tubing into the upper GI tract. (Courtesy of Dr. A. Leland Albright.) (c) Protrusion of distal tubing through the anus due to migration of distal tubing into the lower GI tract. (Courtesy of Dr. A. Leland Albright.)

usually suffice^{34,55} however, in a patient with a more generalized peritonitis, the absorptive capacity of the peritoneum may have been impaired, and drainage to the atrium or pleural cavity may have to be considered.

Distal infection of a ventriculopleural shunt may also result in impaired CSF absorption—in this instance resulting in shortness of breath, pleuritic chest pain, and empyema. Acute ventriculoatrial shunt infection will present with pyrexia secondary to bacteremia; however, a more specific syndrome of “shunt nephritis” may occur in the context of more chronic ventriculoatrial shunt infection.⁵⁶ This is an immune complex-mediated glomerulonephritis most commonly occurring in association with *Staphylococcus epidermidis* shunt infection; it presents with rash, arthropathy, hematuria, and renal insufficiency and can progress to renal failure if the underlying infection is not adequately treated.

Unusually, the shunt may erode through the skin, bladder, bowel, or oral cavity. In such circumstances, the tubing must be considered contaminated and the patient at high risk for progression to CSF infection, necessitating removal of the shunt and replacement with external ventricular drainage pending the results of CSF analysis (► Fig. 77.1b,c).

77.6 Diagnosis of Shunt Infection

There is no universally agreed-upon definition of shunt-related infection. A distinction should be drawn between superficial wound infections, deep incisional infections (that do not penetrate to the CSF or to the distal compartment of drainage), and “organ space” infections; the latter include classic shunt/CSF infections and isolated peritoneal infections. There is little doubt that incisional infections portend a high risk for subsequent shunt infection, although if identified and treated promptly, they may be adequately managed without recourse to removal of the shunt.

A positive CSF culture is the most definitive diagnostic criterion for shunt infection and whenever possible should be sought before treatment is initiated. However, organisms responsible for shunt infection grow in culture at different rates, and it is worth noting that 25% of CSF cultures from hardware take at least 3 days to become positive.⁵⁷ Culture for at least 10 days has been recommended, and for some organisms extended culture beyond this time will be required. Bacteriologic culture results often need to be interpreted with caution and in conjunction with microbiological advice because culture results are influenced by the method of collection and processing, the availability of repeated sampling, and the prior use of antibiotics. For example, inadequate attention to aseptic technique at the time of sampling can result in false-positives due to contamination with skin commensal bacteria, and false-negatives may result if empiric antibiotic therapy has been commenced before CSF sampling. Additionally, isolation of the infecting agent can prove difficult, particularly in the case of low-grade pathogens such as propionibacteria in an abdominal pseudocyst, which may require prolonged anaerobic culture.

77.6.1 Diagnostic Studies

Blood investigations usually reveal a raised polymorphonuclear leukocyte count,⁵⁴ and the serum level of C-reactive protein (S-CRP) will commonly be raised in the presence of shunt infection.⁵⁸ In one study of children with suspected shunt infection, elevated S-CRP showed 97.1% sensitivity and 73.5% specificity for the presence of shunt infection.⁵⁸ The negative predictive value of S-CRP in this study was 97.3%, so a normal S-CRP level may obviate the need for shunt tap in borderline cases, at least in the initial phase of investigation. S-CRP is also useful as an additional parameter by which to monitor the response to treatment. Blood cultures are usually not positive in ventriculo-

peritoneal shunt infections but can be useful in the evaluation of suspected ventriculoatrial shunt infection.

Where wound discharge or other signs of wound infection are present, microbiological swabs should be taken. Additional investigations, including urinalysis and possibly chest X-ray, should be considered in the search for alternative causes of fever.

Although not necessarily of diagnostic value per se in the context of shunt infection, computed tomography or magnetic resonance imaging of the brain should be performed because shunt obstruction may coexist with shunt infection, and in the event that the shunt has to be replaced with an external ventricular drain, knowledge of the ventricular configuration is essential; it may have changed significantly since the initial shunt placement. In patients with complex shunt histories and multiple revisions, X-rays of the shunt system will not only provide evidence of continuity of the shunt system but also serve as a means of looking for lost or retained shunt tubing, which will require removal along with the shunt to eradicate shunt infection.

Samples of CSF for culture should be obtained not only to establish the diagnosis but also to ascertain microbiological sensitivities in order that appropriate antibiotic therapy can be selected. The percutaneous aspiration of CSF from the shunt system with strict aseptic technique is the most usual method and has a high diagnostic sensitivity compared with lumbar puncture or ventricular tap.⁵⁹ The percutaneous aspiration of shunt reservoirs, although generally safe,⁶⁰ carries some risk for introducing infection and should therefore be performed only when there is reasonable clinical suspicion of shunt infection and after other causes for the clinical presentation have been excluded. In cases of abdominal CSF collections, ultrasound-guided aspiration of CSF can be performed, although in this instance the likelihood of infection is sufficiently high to justify proceeding with externalization of the shunt, which affords the opportunity to aspirate CSF via the distal tubing at the time of surgery.

77.7 Treatment of Shunt Infection

Like with most aspects of this subject, the optimal treatment of shunt infection is controversial, and each of the treatment strategies advocated has its advantages and disadvantages. There are two principal points of contention— firstly, whether intraventricular as well intravenous antibiotics should be used, and secondly, whether or not the shunt should be removed.

77.7.1 Antibiotic Therapy

Intravenous and Intraventricular Antibiotic Therapy

Because CoNS are the most common infecting pathogens, and given the high rates of methicillin resistance of these organisms (60%) in hospital practice, a glycopeptide antibiotic (vancomycin or teicoplanin) is generally considered first-line empiric therapy. However, penetration of the blood–brain barrier by this group of drugs is variable, particularly when there is minimal inflammation, so that intravenous and intrathecal administration is advocated. The dosage should be guided by the regular monitoring of levels to ensure an adequate minimum inhibitory concentration (MIC) while avoiding toxicity. If no intraventricular access is available, intravenous vancomycin

should be supplemented with an additional central nervous system–penetrating drug, such as rifampicin or linezolid. Newer agents, such as linezolid, have good CSF penetration and are a suitable alternative for gram-positive infections, particularly in refractory cases or cases with resistance to first-line antimicrobials.^{61,62} Empiric treatment for a gram-negative infection should be given if one is suspected (if the child is severely systemically unwell, if gram-negative organisms have been seen on CSF examination, or if local epidemiology indicates a high rate of gram-negative infection). An appropriate agent would be a third-generation cephalosporin (if local surveillance data do not show a high rate of extended-spectrum β -lactamase-positive organisms) or a carbapenem, with or without an aminoglycoside. Aminoglycosides also have variable penetration of the blood–brain barrier, so intravenous gentamicin may be supplemented with intrathecal gentamicin when there is a susceptible isolate. Clearly, once an isolate has grown, the antibiotic choice may be modified according to sensitivities.

Factors Influencing the Choice of Antibiotic

The following factors need to be accounted for in choosing an appropriate antibiotic regime:

1. The likely causative organisms. When possible, the CSF should be sampled before antibiotics are started. Broad-spectrum antibiotic cover can then be commenced pending the results of culture and sensitivity tests. The empiric antibiotic policy will need to reflect the commonly seen shunt-infecting organisms in the neurosurgical institution (► Table 77.3). In developing countries, the prevalence of gram-negative shunt infection is such that this might need to be reflected in the choice of empiric therapy—for example, the addition of ceftriaxone, another third-generation cephalosporin, or a carbapenem. (Chloramphenicol can be used if other drugs are not available.)
2. The clinical condition of the child and local signs of sepsis. In an acutely unwell child, broad-spectrum antibiotics may have to be started before CSF sampling to include empiric cover for sepsis appropriate to the age of the child.
3. Colonization with known antimicrobial-resistant microbial flora (e.g., methicillin-resistant *S. aureus* [MRSA], extended-spectrum β -lactamase–producing Enterobacteriaceae).
4. Whether or not the shunt is to be immediately removed.
5. Whether intraventricular access will be available.
6. Local antimicrobial availability.
7. A history of antibiotic allergy.
8. Local patterns of antibiotic resistance.

Pediatric neurosurgical units should develop an agreed-upon treatment policy in conjunction with their microbiologists and infectious disease experts. An example of the treatment policy at our institution is shown in ► Table 77.3.

77.7.2 Surgical Management

With respect to the surgical management of shunt infection, three treatment options have been debated: (1) antibiotics, shunt removal, and placement of an extraventricular drain (EVD); (2) antibiotics, shunt removal, and immediate shunt replacement; and (3) antibiotics only.

Table 77.3 Antibiotic therapy for staphylococcal infection following complete shunt removal with external ventricular drains in situ

Drug	Route of administration	Dose		Therapeutic monitoring	Duration of therapy
Vancomycin	Intraventricular (intrathecal)	Preterm	2 mg daily	CSF levels early each morning; dose only to be given if level < 15 mg/L	Minimum 10 day period following the first negative CSF cultures
		Term–3 months	2.5 mg daily		
		3–6 months	3 mg daily		
		>6 months	5 mg daily		
Vancomycin	Intravenous	See GOS vancomycin guideline and note 6 hour dosing is NOT routinely used alongside intraventricular (intrathecal) vancomycin			

- Initial therapy will be with intraventricular (intrathecal) vancomycin and intravenous vancomycin. This will be subsequently modified according to sensitivity results.
- Directed therapy:
 - *S. epidermidis* and *S. aureus* resistant to flucloxacillin or gentamicin. Continue intravenous and intraventricular vancomycin therapy.
 - *S. epidermidis* or *S. aureus* sensitive to flucloxacillin and gentamicin. Stop vancomycin and change to intraventricular gentamicin plus intravenous gentamicin and cefuroxime.

Antibiotics, Shunt Removal, and Temporary External Ventricular Drainage

This strategy is generally accepted as the current standard of treatment.^{63–65} Only one randomized study has compared the three treatment options, and although the numbers were small, all infections in the removal-plus-EVD group were successfully treated with the shortest hospital stay.⁶⁶

A literature review (not exclusively pediatric) comparing the different modalities of treatment of shunt infection identified 11 studies (224 patients) in which the strategy of shunt removal plus EVD had been used.⁶⁷ The total infection cure rate was 87.7% (95% CI, 83.0 to 91.3), and the mortality rate was 5.7% (95% CI, 3.5 to 9.4). This regime entails at least two surgical procedures and potentially additional surgical incisions because some surgeons like to use separate ventricular sites for the EVD and the definitive shunt. The review concluded that this policy of treatment was superior to the other treatments, assuming that the complication rate of EVD was below 35.8%.

The extirpated infected shunt should be sent for microbiological analysis. It is important that all shunt tubing be removed because retained catheters may harbor bacteria and result in treatment failure (► Fig. 77.2).

The EVD may be placed through the same bur hole, with the opposite side left available for final placement. Prolonged duration of external drainage is a risk factor for secondary infection and drainage may be required for up to 3 weeks in severe gram-negative infections, so that our preference is for a long, tunneled EVD exiting through the chest or abdominal wall. A Rickham reservoir at the bur hole site satisfactorily anchors the drain, preventing migration (which can be a problem in children); it can also be used for the intrathecal instillation of antibiotics, although our usual practice is to inject through a three-way tap incorporated into the externalized drainage system. Management of the EVD requires diligent nursing care, and the system should be accessed only as necessary and with strict aseptic technique. The CSF is sampled to evaluate the response to treatment (white cell count and Gram stain) and to monitor levels of intrathecal antibiotic. Liaison with a microbiologist is essential throughout treatment for determining the optimal antibiotic regimen and duration of therapy.

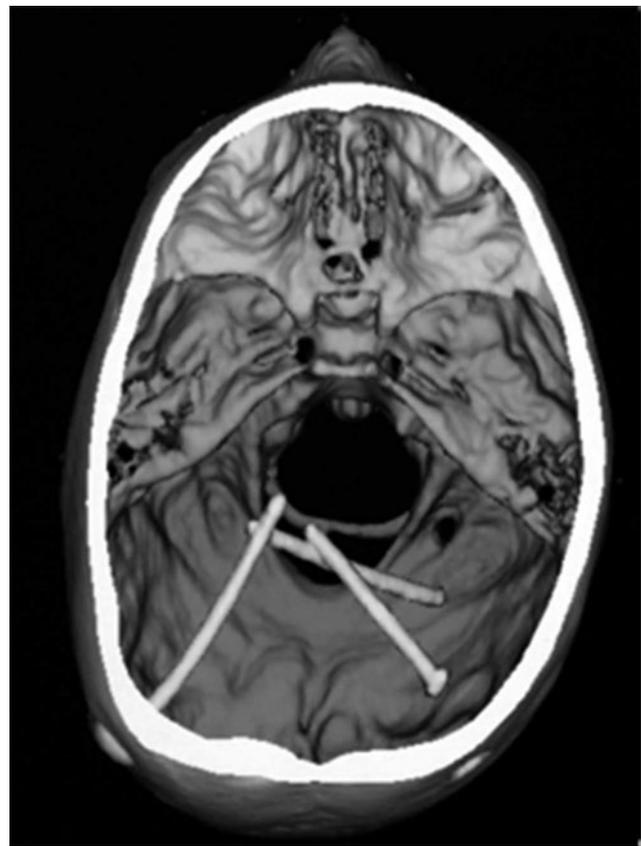


Fig. 77.2 Retained shunt tubing. 3D CT scan showing retained ventricular catheters. Successful treatment of a shunt infection requires the removal of all catheter tubing.

Re-internalization should be delayed until the CSF cultures are sterile and antibiotic therapy is complete. There is no consensus on duration of therapy,⁶⁴ and factors to be considered include the infecting organism, the response to treatment, and the quality of the CSF. CoNS infections usually respond promptly to therapy, whereas *S. aureus* and gram-negative infections may take longer to clear from the CSF. Surgeons are more likely to use external drainage during therapy and a

longer total duration of therapy when dealing with these organisms.^{64,68} A period “off antibiotic therapy” to ensure sterility at the end of treatment increases the risk for reinfection and is generally not warranted. Before re-internalization, elevating or clamping the EVD for up to 12 hours before surgery can make ventricular cannulation easier. Because there is a risk for contamination along the EVD track, many prefer to use a fresh site for the new shunt.

Antibiotics, Shunt Removal, and Immediate Shunt Replacement

The main advantage of this option is that it obviates the need for a second surgical procedure. However, the CSF may not be sterile at the time of insertion, and an elevated CSF cell count may increase the risk for blockage. Intraventricular antibiotic administration in this scenario is more invasive, necessitating ventricular tap or puncture of the shunt reservoir. In the review by Schreffler et al, the cure rate for shunt infection with this regimen was 64.4% (95% CI, 54.2 to 73.6), and the mortality was 11.1% (5% CI, 6.2 to 19.3).⁶⁷ This strategy is reported to have a better outcome with low-virulence, slow-growing organisms such as *P. acnes*.⁶⁹

Antibiotics Alone

This option can be considered only when the shunt remains functional. It has the advantages of avoiding multiple surgical interventions, reducing hospital stays, and lowering treatment costs. In a review of the literature, the cure rate for antibiotics alone was 33.5% (95% CI, 27.7 to 39.4), and the overall mortality was 20.4% (95% CI, 15.7 to 26.1).⁶⁷ Given the propensity of the most commonly implicated organisms to form a biofilm, this high failure rate is perhaps unsurprising; however, Brown et al argued that the failure rate associated with this conservative regime was due to suboptimal antibiotic therapy. With a combination of oral or intravenous rifampicin and intrathecal vancomycin (via a separate subcutaneous reservoir), they reported an 84% cure rate.⁷⁰ Interestingly, their regime was more effective in CoNS infections than *S. aureus* infections.

Experimental data have recently been published to support the potential use of linezolid alone, without shunt removal, and this may be an option in some cases.⁷¹

There are special circumstances in which the occurrence of a central nervous system infection in a child with a shunt does not mandate removal of the shunt. These include cases of meningitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Neisseria meningitidis* and of tuberculous meningitis in which appropriate medical therapy alone will usually suffice.^{72,73}

The development of a non-shunt-related abdominal or pelvic infection (e.g., appendicitis) has the potential to cause ascending infection and ventriculitis; however, there is no consensus regarding the optimal management of the shunt in this circumstance. In cases of appendicitis, the traditional view has been to recommend externalization of the shunt pending appendectomy and comprehensive treatment of the underlying infection^{74–76} however, more recent studies suggest that leaving the shunt in situ is a safe option so long as the underlying

infection is aggressively treated.^{77,78} In the absence of a clear evidence base, it seems appropriate to suggest that cases be managed on an individualized basis. If the shunt is left in situ, it is essential that the patient's condition be carefully monitored until the septic episode has resolved. The potential for distal shunt malfunction as well as ascending infection must be kept in mind.

Treating Gram-Negative Infection

Gram-negative infections, most commonly with *Pseudomonas aeruginosa* or Enterobacteriaceae (e.g., *Escherichia coli*), are especially serious infections in children, with high morbidity and mortality rates. Antibiotic resistance is increasingly common, the CSF is slow to sterilize, and relapse may occur. Infection should be managed in conjunction with the infectious disease and microbiology service, and although there is no consensus, we advise a minimum of 3 weeks of intravenous therapy, with additional intraventricular aminoglycoside before sensitivities are available and at least until the CSF is culture-negative. The duration of intraventricular therapy is managed on an individual basis. Failure to clear infection may result from underdosing (it is important to ensure that all cephalosporins or carbapenems be given at full “meningitis” dose), abscess formation or loculation, or infection of the EVD. Further surgical management may be necessary, including change of the EVD, during treatment.

77.7.3 Outcome

Despite the apparent efficacy of first-line therapy for shunt infection, repeated infections do occur, representing either a relapse of infection with the original organism due to treatment failure or reinfection with a new organism following shunt replacement. This remains an issue and may be overlooked in studies with inadequate follow-up. Repeated infection rates of 19.6% and 26% have been reported in two North American studies.^{46,47} A distinction should be drawn between treatment failures and reinfections. In the study by Kestle, two-thirds of the repeated infections were with the same organism, suggesting a failure of primary treatment (relapse).⁴⁷ No consistent risk factors have as yet been identified to explain the high rate of repeated infections.

An 10-year audit of the outcome of treatment according to the strategy described for our own institution showed that of 105 shunt infections, 2 were relapse infections (each a deep incisional and CSF infection with *S. aureus*). There was no relapse of an original CoNS infection, but reinfection occurred at a rate identical to the prevailing shunt infection rate at the time of the audit (unpublished data).

77.8 Prevention

77.8.1 Antibiotic Prophylaxis

Because shunt infections frequently arise from bacterial contamination at the time of insertion and are not eliminated by the usual host defense mechanisms, a logical prevention

strategy is the administration of prophylactic antimicrobials. These may be given systemically or locally; local administration may be by direct instillation or by incorporation into implanted materials.

A number of randomized controlled clinical trials have sought to demonstrate the efficacy of systemic antibiotic prophylaxis in shunt surgery, unfortunately with variable conclusions. Because most centers have shunt infection rates of 10% or less, single-institution studies are often insufficiently powered to reach a significant conclusion. It has been calculated that for a study to have an 80% chance of detecting a decrease in the infection rate from 10 to 8.4%, a sample size of more than 8,000 patients is required.⁷⁹ Meta-analysis seeks to overcome the problem of sample size by aggregating the results of multiple smaller studies. Two such analyses have been performed, both finding in favor of the use of prophylaxis.^{79,80} Haines and Walters examined the results of 9 randomized studies and found that the combined infection rates for 527 controls and 516 treated patients were 13% and 7%, respectively. This apparent benefit of prophylaxis was, however, related to the baseline infection rate and was lost if the baseline rate was less than 5%.⁷⁹ The use of intravenous antibiotic prophylaxis for shunt surgery is now almost ubiquitous among neurosurgeons; however, significant variation in practice remains regarding the choice of antibiotic and duration of prophylaxis.¹⁴ Additional measures, such as soaking the shunt in antibiotic solution or administering antibiotic intraventricularly as well as intravenously, are commonplace but have not been demonstrated to provide additional benefit.

Surgeons should be encouraged to engage with microbiologists in their institutions to agree on the details of prophylaxis. Antibiotics should be administered at the time of induction of anesthesia, and the duration of prophylaxis should not exceed 24 hours.

77.8.2 Antibacterial Shunt Technology

Modifying shunt catheters to make them less susceptible to bacterial adhesion and to deliver antimicrobials locally, thereby reducing the chance for shunt infection, has been the source of much research during the past two decades. Broadly speaking, these modifications involve the incorporation of one or more antimicrobial agents into the catheter, either by *coating* the catheter (hydrogel, heparin, or silver) or by *impregnating* antibiotics into the biomaterial during the manufacturing process.²⁹ It is important that the antimicrobial effect of these catheters persist well into the postoperative period if shunt infection is to be prevented. In many cases, *in vitro* results have been encouraging; however, because of the effects of CSF flow, protein deposition, and other factors, efficacy may be compromised in the *in vivo* situation.

Antibiotic-Impregnated Shunts

More than 20 years ago, Bayston demonstrated that the antibiotics clindamycin and rifampicin could be incorporated into Silastic (Dow Corning, Midland, MI) shunt tubing, and an

antibiotic-impregnated shunt (Bactiseal; Codman & Shurtleff, Raynham, MA) has been commercially available since 2002. A number of advantages have been cited. The antibiotic combination is effective against the most common gram-positive shunt-infecting organisms; slow elution from all surfaces of the catheter reduces the potential for bacterial colonization, not only on the external surface of the shunt but also within the lumen; and antibiotic-impregnated shunts continue effective antistaphylococcal activity well into the postoperative period. *In vitro* studies have demonstrated effective protection against a range of *S. aureus* organisms and CoNS for between 42 and 56 days,⁸¹ and *in vivo* studies of explanted shunts suggest that the duration of activity may be substantially longer⁸² (► Fig. 77.3).

A number of attempts have been made to evaluate the effectiveness and economic impact of antibiotic-impregnated shunts. Most of the information is from retrospective studies, and although most indicate a favorable reduction in the shunt infection rate,⁸³ this is not universally the case; as with many shunt infection studies, interpretation of the data is not infrequently constrained by methodologic flaws, including small sample size and inconsistent definitions of shunt infection. Two meta-analyses have been undertaken, both including data from adult and pediatric practice. Both conclude that antibiotic-impregnated shunts are associated with a significant reduction in shunt infection compared with non-antibiotic-impregnated shunts.^{83,84} Klimo et al concluded that the risk for developing a shunt infection with a standard shunt was 2.18 times greater than that with an antibiotic-impregnated shunt. When analyzing the pediatric data separately, Parker et al found a shunt infection rate of 5.0% for antibiotic-impregnated shunts compared with 11.2% for non-antibiotic-impregnated shunts ($p < 0.0001$).⁸⁴ Our own experience concurs with this finding; we experienced a shunt infection rate of 5.1% while using antibiotic-impregnated shunts, compared with 8.35% in our historical control. Interestingly, in the historical series, CoNS infections comprised 51.9% of the infections, compared with 16% in the antibiotic-impregnated shunt group. Larger prospective series will be needed to ascertain whether the microbiological profile of shunt infections will be altered by the more widespread use of antibiotic-impregnated shunts. Although there had been concerns that the use of antibiotic-impregnated shunts might promote the emergence of drug-resistant bacteria, currently there are no reliable data to support this assertion.

The cost of antibiotic-impregnated shunts is greater than that of conventional shunts; however, when institutions have an infection rate of greater than 5%, the savings achieved by avoiding the costs of treating shunt infections make antibiotic-impregnated shunts cost-effective.^{83,85} Both meta-analyses acknowledge the limitations of these conclusions and point to the need for a randomized control clinical trial. The BASICS trial, a national, randomized trial of antibiotic-impregnated, silver-impregnated, and standard silicone shunts, opened in the UK in 2013.

Silver-Impregnated Catheters

Silver has a broad antimicrobial spectrum, and this property has been put to use in urinary and vascular catheters with some

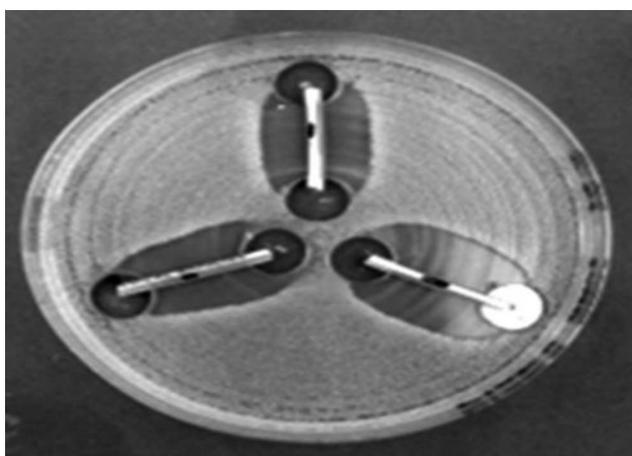


Fig. 77.3 In vitro study demonstrating zones of inhibition of bacterial growth around antibiotic impregnated shunt tubing. (Courtesy of R. Bayston.)

effect. Silver has been incorporated into shunt catheter tubing and is now commercially available (Silverline; Spiegelberg, Hamburg, Germany). Although silver-impregnated tubing is licensed for incorporation into shunt systems, most of the current data pertain to EVD use, in which clinical studies have suggested a statistically significant reduction in CSF colonization compared with controls.^{86,87} Licensing data demonstrate in vitro antimicrobial activity, although an in vitro test model that used inocula much higher than are likely to be encountered in vivo demonstrated that silver catheters were unable to eradicate MRSA or *E. coli* and had limited activity against *S. epidermidis*.⁸⁸ However, a recent randomized trial of EVDs also demonstrated that silver-impregnated tubing produced a highly statistically significant reduction in infection from 21.4% in the control group to 12.3% in the silver catheter group.⁸⁹ There are currently insufficient data to evaluate the efficacy of silver catheters in shunt (rather than EVD) systems.

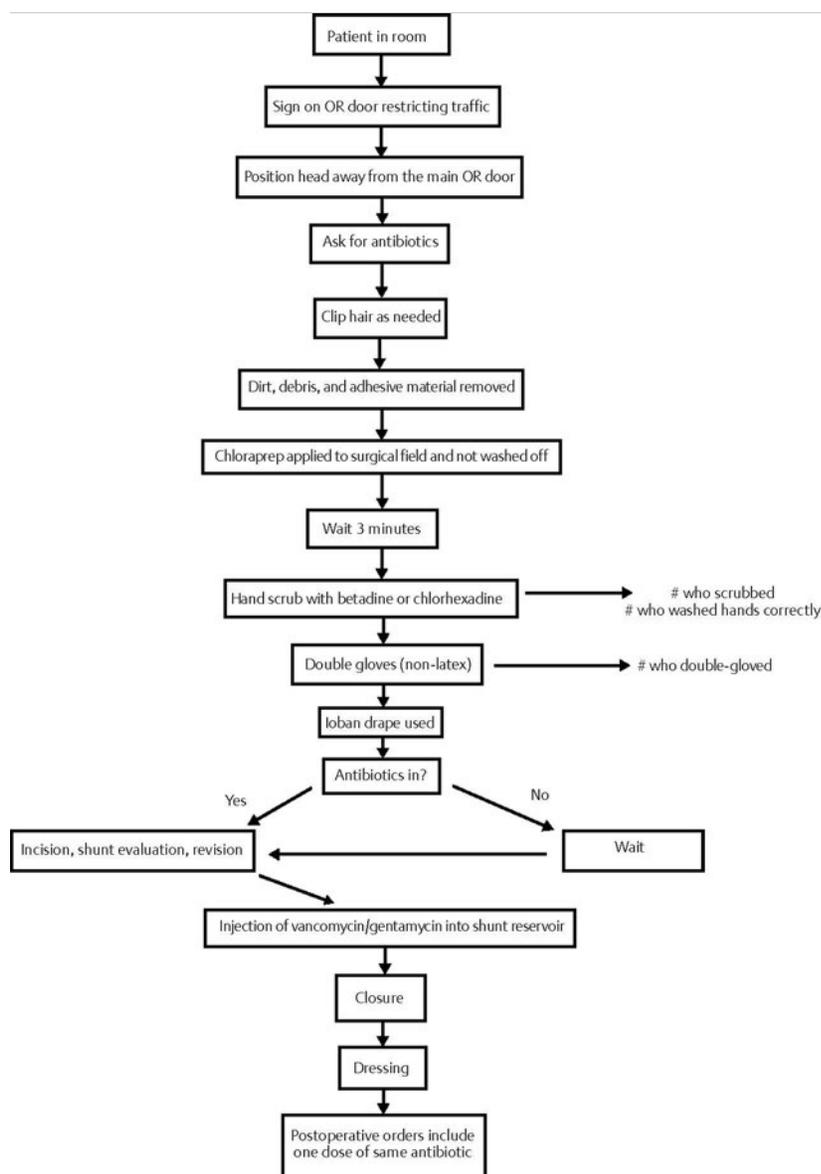


Fig. 77.4 Shunt insertion protocol developed by Hydrocephalus Clinical Research Network.¹¹

Hydrogel-Coated Catheters

In these catheters, a hydrophilic polymer (BioGlide; Medtronic, Minneapolis, MN) is used to coat the catheter surface. Before insertion, the tubing is soaked in water; the polymer swells and thus creates a hydrophilic surface that will impair bacterial adherence. It has been proposed that the addition of antibiotics, which can be absorbed into the polymer, to the soaking solution will confer some further antibacterial activity following insertion. In vitro studies have confirmed reduced bacterial adhesion on hydrogel-coated catheters; however, soaking the catheters in an antibiotic solution failed to prevent bacterial colonization.⁹⁰ In clinical studies of hydrogel catheters, the results have thus far been disappointing. EVD infection rates were not reduced by hydrogel-coated catheters.⁹¹ Few studies have examined hydrogel-coated shunt systems; however, in a recent large study by the Hydrocephalus Clinical Research Network, regression analysis revealed that the use of BioGlide shunts was associated with an increase in the shunt infection rate.⁶⁵

77.8.3 Protocols for Shunt Insertion

Twenty years ago, Choux et al demonstrated that if relatively modest changes to the pre-, intra-, and postoperative management of children undergoing shunt surgery were made and incorporated into a protocol, the goal of a zero rate shunt infection could be achieved.² The importance of surgical training and experience, in addition to strict adherence to a no-touch technique, careful tissue handling, and careful wound closure, in reducing shunt infection rates cannot be overemphasized; however, infection rates that differ between surgeons and centers suggest an ongoing need for unified shunt protocols.¹⁵ It may not be possible for all elements of a protocol to be supported by level 1 evidence; however, as demonstrated by the Hydrocephalus Clinical Research Network, the introduction of a consistent, reproducible, and carefully audited protocol for shunt placement can significantly reduce shunt infection rates (► Fig. 77.4).⁶⁵ When applied across large clinical networks, such a protocol establishes a baseline from which it becomes feasible to begin to evaluate critically and in a statistically more meaningful way not only the causative factors for infection but also the results of interventions designed to reduce infection rates still further.

Given the economic burden and the clinical consequences of shunt infection, it is clear that it is imperative for all shunt surgeons to critically evaluate their own practices and engage in local multidisciplinary surveillance and data collection.⁹² Local practice can be scrutinized and clusters of shunt infection can be identified early, permitting the immediate investigation of causative factors. Only through such transparency and reflection will the morbidity of shunt surgery be reduced.

Pearls

- The majority of shunt infections are caused by commensal skin organisms, the most prevalent being *S. epidermidis*.
- Shunt infections are a complication of surgery; over two thirds of shunt infections are diagnosed within two months of surgery. The majority of shunt infections should be considered a failure of surgical technique.
- Wound-related complications, particularly wound infection or CSF leakage, are the strongest risk factors for shunt infection.
- In cases of suspected shunt infection, CSF sampling should be performed prior to commencement of antibiotic therapy and only after other sources of fever or infection have been excluded.
- Shunt removal, followed by temporary external CSF drainage combined with selective antibiotic therapy, is the most effective strategy for treatment of shunt infection.
- Preliminary studies indicate that antibiotic impregnated shunts reduce shunt infection rates, though randomized clinical trials are required to validate this observation.
- The introduction of shunt insertion protocols has been shown to reduce shunt infection rates. Prospective audit of shunt infection is recommended in order to monitor shunt infection rates and to identify clusters of shunt infection that might require more detailed analysis.

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78 Cranial Epidural Abscess and Subdural Empyema

Christine L. Hammer and Joseph H. Piatt Jr.

Epidural abscess and subdural empyema are central nervous system infections that arise as infrequent complications of neurosurgical procedures, open trauma, and common infectious processes, such as sinusitis or meningitis. Until penicillin became widely available in the 1940s, mortality from these infections approached 100%. Contemporary reports now cite mortality rates for subdural empyema in the neighborhood of 10%, and mortality from epidural abscess is exceptionally low.¹⁻⁶ Despite the efficacy of modern antibiotic therapy, timely neurosurgical interventions continue to play an important role in the microbiological diagnosis and control of intracranial hypertension. The coordinated multidisciplinary management of these very sick children yields gratifying clinical recoveries in the great majority of cases.

Epidural abscess, also known as extradural abscess or extradural empyema, is a collection of pus between the dura mater and overlying bone. Subdural empyema is suppuration between the cranial dura and arachnoid membranes. Alternative terms include *subdural abscess*, *purulent pachymeningitis*, *intradural abscess*, and *intrameningeal abscess*.^{7,8} Collectively, epidural abscess and subdural empyema are described in this chapter as *extracerebral suppuration*. The term *intracranial suppuration* may be used to encompass brain abscess as well as epidural abscess and subdural empyema. The term *empyema* connotes pus within a preexisting anatomical space, whereas the term *abscess* describes a collection of pus in the parenchyma of a tissue or an organ. *Empyema* might therefore be an appropriate term for epidural infection as well, but this chapter conforms to the customary usage, which emphasizes the common focality of epidural pus versus the typically diffuse distribution of subdural pus. This distinction also serves to emphasize the relative benignity of infection limited to the epidural space, as will be seen.^{6,7,9}

78.1 Epidemiology

Little is known about the incidence of extracerebral suppuration in childhood. A population-based study drawing on administrative data sets in the United States estimated the annual incidence of hospital admission for intracranial suppuration, including brain abscess associated with sinusitis or otitis, to be between 3 and 4 per million children per year, but this study did not encompass posttraumatic or postsurgical cases or cases of subdural empyema complicating infantile meningitis.⁶ The largest case series of extracerebral suppuration have been reported out of Africa and southern Asia,^{1,2,10-23} but whether these impressive clinical experiences reflect a greater burden of disease or referral to a more limited number of neurosurgical centers from wider geographic regions is impossible to determine. The relative frequencies of epidural abscess and subdural empyema have not been studied in epidemiologic terms, but case series that include both entities tend to cite comparable numbers of each.^{3,8,9,11,24-28} Exceptions are several large case series from Africa that show a marked predominance of subdural empyema.^{2,13,22} Mixed epidural and subdural infections and

associated brain abscesses are not uncommon.^{3,11,27,29-31} Empyema associated with infantile meningitis is exclusively subdural. The etiology of the infection determines the typical age at presentation. Subdural empyema complicating meningitis is a phenomenon of infancy and early childhood.⁸ The incidence of intracranial suppuration complicating sinus and ear disease peaks in mid adolescence.^{2,6,11,13,22,32-34} Regardless of the etiology, a male predominance has been observed consistently at a rate of roughly 2:1.

The dominant etiology of epidural abscess and subdural empyema in childhood is extension from head and neck infection. The facial sinuses, middle ear, and mastoid sinus are the most common primary sites. Subdural empyema complicating dental infection has been reported, but in distinction to its prominent role in the etiology of brain abscess, it accounts for a negligible fraction of cases of extracerebral intracranial suppuration.^{2,35,36} In infancy and early childhood, subdural empyema is seen most commonly as a complication of meningitis.^{8,11,32,37} The following discussion proceeds along these etiologic lines. Posttraumatic and postsurgical infections are fortunately infrequent and are necessarily contingent on preceding trauma or surgery. They are considered only very briefly.

78.2 Sinusitis and Ear Disease

78.2.1 Incidence

Sinusitis and ear disease are very common in childhood, but the incidence of these conditions is poorly defined. The clinical diagnosis is imprecise, and many cases escape medical attention altogether.^{5,28,38} Outpatient management is the rule, and only a small but unknown fraction of patients are admitted to a hospital for parenteral antibiotics. Among 649 patients of all ages hospitalized for sinusitis, Clayman et al recorded intracranial complications, including brain abscess and meningitis as well as extracerebral abscess, in 24 (3.7%).³⁸ Analysis of the 2009 Kids' Inpatient Database (KID) disclosed an estimated 10,906 nationwide admissions with a primary diagnosis of sinusitis, otitis, or mastoiditis. That year, there were an estimated 443 admissions for intracranial suppuration of all types associated with sinusitis or ear disease, for a rate of 4.1% (J.H.P., unpublished data). Thus, the incidence of extracerebral suppuration complicating sinusitis or ear disease can be taken to be less than 1/25th the incidence of hospitalization for these conditions and to be a very tiny fraction of the overall incidence. The miniscule incidence of intracranial suppurative complications of sinusitis has frustrated efforts to prevent them.

78.2.2 Mechanism

Extracerebral suppuration is usually associated with sinusitis involving the frontal or ethmoid sinuses.^{7,39} The next most commonly involved sinus is the mastoid.⁴⁰

Speculation about the mechanisms of spread of infection from the sinuses to the epidural and subdural spaces has been

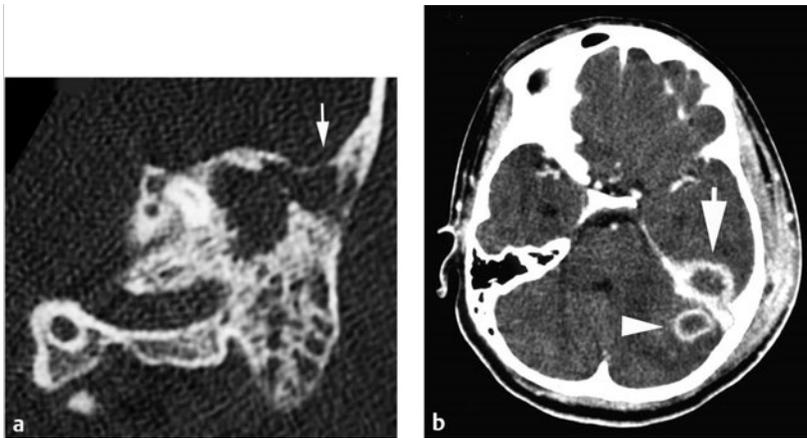


Fig. 78.1 (a) Computed tomographic (CT) scan of the temporal bone of a child with otitis and mastoiditis shows opacification of the antrum and mastoid cells with erosion of the tegmen tympani (white arrow). (b) CT scan of the brain with enhancement in the same patient demonstrates a small abscess in the left cerebellar hemisphere (white arrowhead) and an extracerebral abscess on the floor of the middle fossa (white arrow). At surgery, the middle fossa collection proved to be epidural. (Courtesy of Drs. Joseph Piatt, Jennifer Smith, and Eric Faerber.)

based on gross observations at surgery and at autopsy. Seldom are macroscopic defects observed in the posterior wall of the frontal sinus or the roof of the ethmoid sinus, but in the setting of chronic otitis and mastoiditis, destruction of the roof of the middle ear, the tegmen tympani, can be seen in association with epidural pus on the floor of the middle fossa (► Fig. 78.1a, b). The perforations of the cribriform plate have been mentioned as possible portals for entry of infection, but they are likely more relevant to the pathogenesis of meningitis than of extracerebral suppuration. In the absence of an osseous defect, infection is commonly believed to spread by septic thrombophlebitis of the transosseous venous channels. Spread through the dura may occur on a similar basis. At autopsy, frank necrosis of the dura has been observed adjacent to an infected sinus, accounting for some instances of the breach of what is usually a very stout barrier to the spread of infection.⁷ Septic thrombosis of cortical bridging veins and adjacent dural venous sinuses is more likely a complication of advanced subdural empyema than a mechanistic cause.

78.2.3 Predisposing Factors

Male sex, black race, and age in the early teens seem to impart a vulnerability to intracranial suppurative complications of sinusitis and ear disease. The developmental, anatomical, and physiologic mechanisms underlying these associations have been the subject of speculation, but they are unknown.^{6,26} Factors that contribute to the development of sinusitis necessarily make indirect contributions to the incidence of its complications. Many studies have described a seasonal pattern that seems dependent on geography. In central Europe, cases of complicated sinusitis peak in the month of March,⁴⁰ and reports from Africa and India find most cases of subdural empyema in their summer months.^{4,10,12} In the United States, winter is the dominant season for sinogenic intracranial suppuration,³⁰ but no seasonal pattern is apparent for otogenic cases.⁶ In view of the anatomical, physiologic, and immunologic continuity of the sinobronchial tree, there has been much discussion of the association of sinusitis with allergy and asthma. A large cohort study in the United States identified a strong association of asthma with sinogenic intracranial suppuration. This association did not hold for ear disease.⁶ The linkage between sinogenic intracranial suppuration and asthma raises questions about the relevance of environmen-

tal factors like air quality.⁴¹ Over the first decade of this century, there has been no clear trend in the incidence of sinogenic intracranial suppuration.⁶ Analysis of the 2009 KID shows that patients admitted with a primary diagnosis of sinusitis, otitis, or mastoiditis came from ZIP codes where the median home income was lower than those for other admissions, but this association was not evident for intracranial suppuration complicating sinusitis and ear disease (J. H. P., unpublished data). Adame and colleagues have discussed a possible linkage of sinogenic empyema with diabetes, another prevalent and chronic condition with social and environmental associations.⁴² Geographic and socioeconomic correlations deserve further study.

78.2.4 Clinical Presentation

The initial clinical presentation of epidural abscess complicating sinusitis or ear disease is indistinguishable from the symptoms and signs caused by the primary infection: headache, fever, sinus pain or tenderness, purulent rhinorrhea or otorrhea, and conductive hearing loss. Only later in the course of the illness, if the epidural collection attains sufficient volume to cause mass effect or if complicating subdural suppuration or cerebral abscess develops, can papilledema, focal neurologic deficits, depressed responsiveness, and seizures appear. A special case is the distinctive clinical syndrome of Pott's puffy tumor (► Fig. 78.2). Named after Sir Percivall Pott, an English surgeon who described this phenomenon in 1760, the puffiness reflects subperiosteal pus and osteomyelitis of the frontal bone complicating frontal sinusitis. It is reliably associated with at least some degree of epidural suppuration, and in more advanced cases, subdural empyema or cerebral abscess may be present as well. Pott's puffy tumor has been described as a historical curiosity,⁴³ but it is certainly a feature of contemporary practice.^{11,25,27,42,44–48} Osteomyelitis of the frontal bone raises particular issues for treatment that are discussed below.

Subdural empyema complicating sinusitis or ear disease may be impossible to distinguish from meningitis in its initial clinical manifestations; fever, headache, lethargy, and meningismus are common. The development of focal neurologic deficits and seizures directs attention to the correct diagnosis. Before the current era of computed brain imaging, the clinical triad of fever, seizures, and hemiplegia was viewed as pathognomonic for subdural empyema.



Fig. 78.2 Computed tomographic scan with enhancement of the brain in a case of frontal sinusitis with Pott puffy tumor. The scan shows a large subperiosteal abscess (asterisk) and a smaller epidural abscess (arrow). (Courtesy of Drs. Joseph Piatt, Jennifer Smith, and Eric Faerber.)

78.2.5 Microbiology

Streptococcus and *Staphylococcus* species are the most common isolates.^{4,5,9–11,13,27–31,33,49–53} Most frequently mentioned by genus and species is *Streptococcus milleri*. In contemporary parlance, this term refers to a group of α -hemolytic viridans streptococci—*Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*, the so-called *Streptococcus milleri* group (SMG).⁵⁴ SMG organisms are typically pyogenic and tend to be found in association with the gastrointestinal tract, oropharynx, facial sinuses, and teeth. Gram-negative organisms, particularly *Pseudomonas*, are prevalent in cases of otogenic suppuration associated with cholesteatoma.^{55,56} The meticulous handling of specimens discloses substantial rates of anaerobic and polymicrobial infection that must be considered in treatment planning.^{29,53,57–59} In geographic regions where it is prevalent, tuberculosis is a possibility as well.⁶⁰ Intracranial pus yields positive cultures in upward of 65% of cases.^{2,4,5,10,11,13,16,25,27,29,31,33,34,44,50–53,57,61}

Once the existence of sinogenic or otogenic intracranial suppuration has been recognized, lumbar puncture is no longer indicated. As a diagnostic priority, lumbar puncture is superseded by the sampling of pus from the intracranial collections and the sinuses, and in the presence of intracranial mass effect, lumbar puncture may be contraindicated because of the risk for herniation, a complication mentioned frequently in the older literature.^{13,62,63} Culture-positive cerebrospinal fluid (CSF) has been reported in fewer than half of cases of subdural empyema, and in many reports the culture yield is nil.^{5,13,20,42,51,52,62,64–66} The

CSF formula generally conforms to a parameningeal pattern: a neutrophil-predominant pleocytosis with elevated protein and normal glucose.⁶² The CSF findings associated with epidural abscess have received little attention in the literature.²

Blood cultures are obtained routinely and have been reported to be positive in up to 40% of cases.^{5,10,27,50,52} Other laboratory studies, such as the white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level, are unlikely to impact the diagnostic process, but they may be useful to follow the response to treatment. Reports from two centers have noted that although the C-reactive protein level and erythrocyte sedimentation rate are consistently elevated in patients with sinusitis, these markers are much higher in cases complicated by intracranial suppuration.^{27,42}

78.2.6 Imaging

The decision for brain imaging in the patient with suspected intracranial suppuration seldom lies in the hands of the neurosurgeon, but for monitoring the patient's response to treatment, computed tomography (CT) and magnetic resonance (MR) imaging both have strengths and weaknesses that must be considered.

CT is adequate for most neurosurgical purposes. Extracerebral suppuration generally exhibits low density compared with brain (► Fig. 78.3a). Epidural abscess has the expected biconcave morphology (► Fig. 78.5), and subdural empyema spreads more widely and conforms more closely to the contour of the adjacent brain. With the administration of contrast, there is pachy- and leptomeningeal enhancement surrounding the collection (► Fig. 78.3b). An advantage of CT is precise demonstration of the osseous anatomy and pathology in the calvaria and in the facial sinuses and temporal bones. The prevailing navigation systems for endoscopic sinus surgery, often undertaken by colleagues in otolaryngology concurrently with the neurosurgical drainage of intracranial pus, rely on CT data sets. A disadvantage of CT is the artifactual image distortion that occurs at the interface between high-density bone and adjacent low-density soft tissue, so-called beam hardening. Unfortunately, in this clinical context the regions of the cranial cavity immediately adjacent to the skull are of paramount interest—the epidural and subdural spaces and the dural venous sinuses. Another potential weakness of axial CT relates to the evaluation of lesions at the vertex of the cranial cavity, a not uncommon site for epidural abscess.⁸ Sagittal and coronal reconstructions obviate this problem. Without a doubt, CT has poorer image clarity and lower sensitivity than MR imaging. When CT is employed as an initial diagnostic test, the occurrence of false-negative results of noncontrast CT must be born in mind,^{27,42,67–69} and if intracranial infection is suspected prospectively, contrast must be administered.⁷⁰

MR imaging offers much more anatomical and physiologic information than CT, but whether this information justifies the additional logistical complexity and commitment of time requires consideration on a case-by-case basis. Epidural and subdural pus are generally low-intensity on T1-weighted and fluid-attenuated inversion recovery (FLAIR) sequences and high- or mixed-intensity on T2-weighted sequences.⁷¹ Enhancement patterns are similar to those on CT (► Fig. 78.3c). Diffusion-weighted imaging (DWI) detects ischemic injury in brain

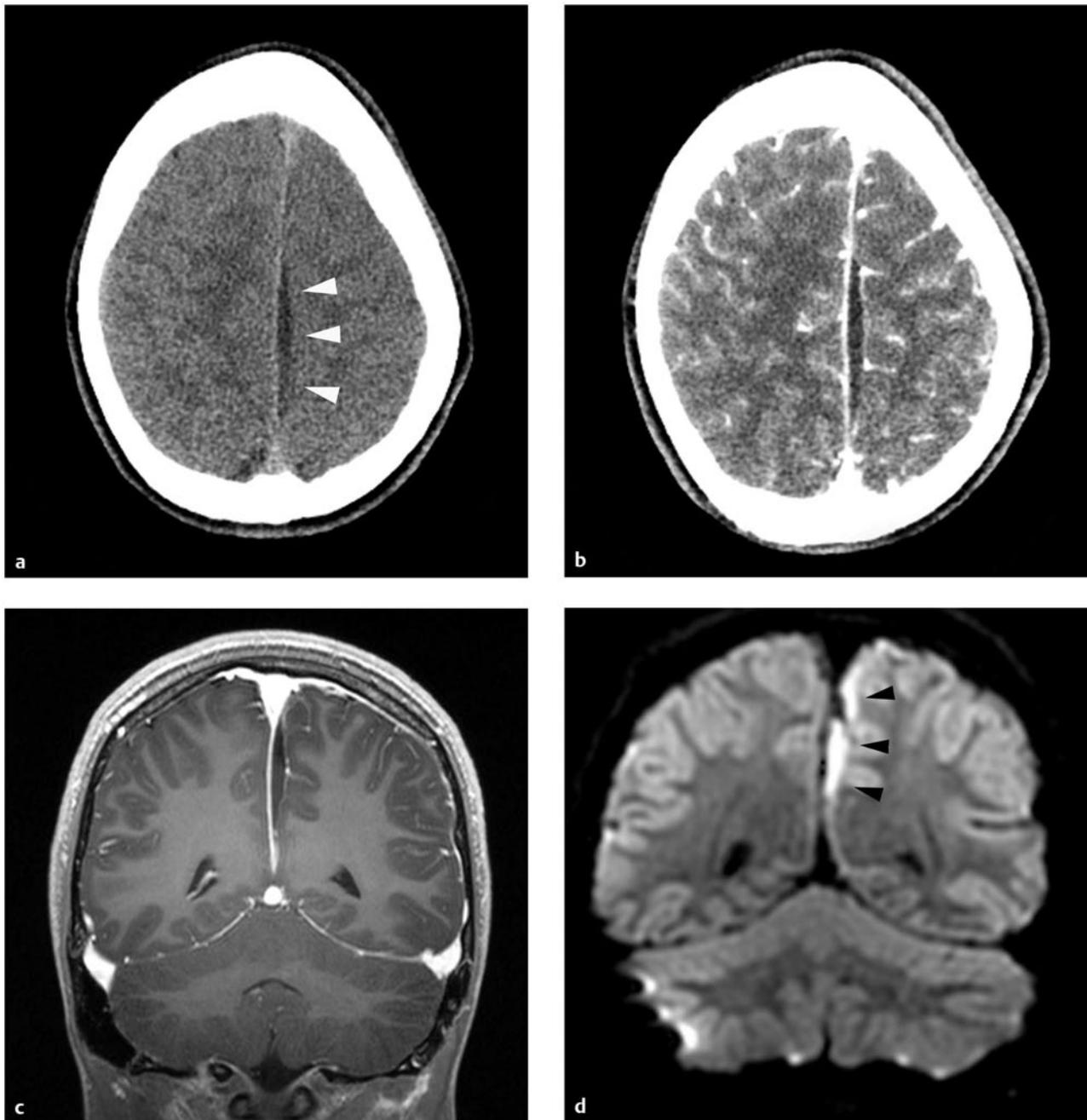


Fig. 78.3 (a) This school-age boy had headache and fever. He was lethargic at presentation, and there was a right lower limb monoparesis. After functional endoscopic sinus surgery for his associated frontal and ethmoid sinusitis, he received a 6-week course of parenteral antibiotics. There was no neurosurgical intervention. He recovered completely. Computed tomographic scan of the brain without contrast shows a small, low-density collection in the interhemispheric fissure (*white arrowheads*). (b) There is pachy- and leptomeningeal enhancement after contrast administration. (c) Likewise, there is pachy- and leptomeningeal enhancement on this coronal, T1-weighted magnetic resonance imaging sequence. The collection itself is low-intensity compared with brain. (d) On diffusion-weighted imaging, the interhemispheric pus is high-intensity (*black arrowheads*).

adjacent to subdural collections, and because the diffusion of water protons is restricted by the viscosity of pus, the collections themselves are distinct high-signal structures (► Fig. 78.3d)^{71–73} Conversely, purulent collections have low intensity on apparent diffusion coefficient (ADC) maps.^{71,72} Epidural abscesses may not restrict diffusion so consistently as subdural collections.⁷⁴ MR spectroscopy detects the elevated

lactate concentrations typical of purulent collections. Arterial spin labeling sequences document cerebral perfusion, and MR venography offers sensitive assessment of the dural venous sinuses. Many of these data, elegant as they are by historical standards, are of limited practical usefulness for treatment planning. The utility of imaging data for the prognostication of functional outcomes has not been analyzed extensively, but

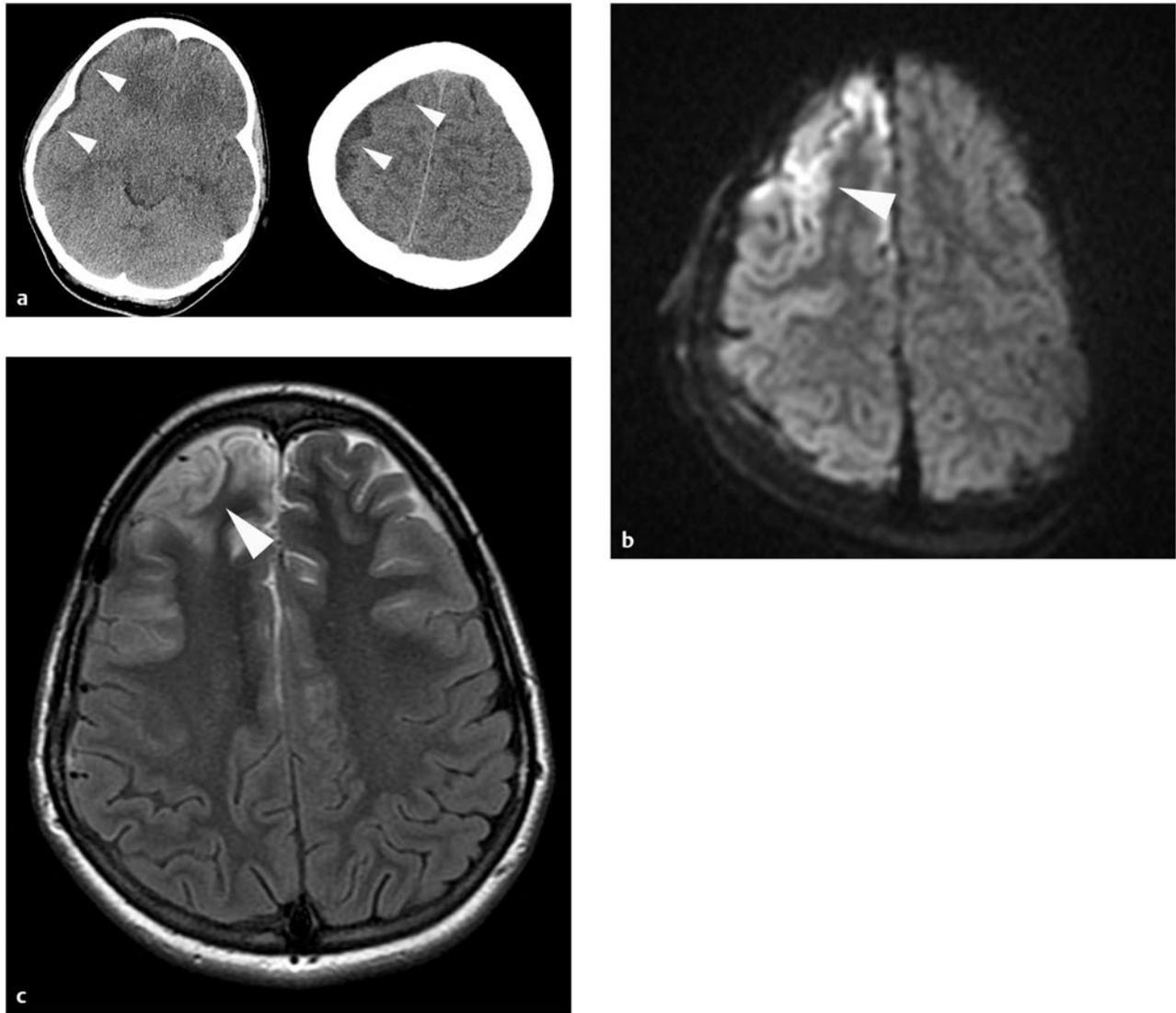


Fig. 78.4 (a) This school-age girl collapsed at home after several days of headaches and fevers. In the emergency department, she was noted to be hemiplegic on the left side. A computed tomographic scan of the head without contrast shows a thin, low-density subdural collection (white arrowheads) distributed widely over the right convexity. She underwent immediate osteoplastic right frontoparietotemporal craniotomy for drainage of her empyema. Her postoperative course was notable for septic shock requiring aggressive fluid resuscitation and pressors. (b) The diffusion-weighted image (DWI) from a study performed on the third hospital day shows high signal intensity in the cortical mantle of the right frontal lobe (*white arrowhead*). (c) At late follow-up, her hemiplegia had resolved completely, but she has persisting neurocognitive disabilities and is continuing in rehabilitation. This T2-weighted axial MR imaging sequence shows encephalomalacia (*white arrowhead*) at the site of the abnormality on the earlier DWI sequence.

patients with cortical ischemic changes on DWI sequences in the acute stages of their illness often exhibit encephalomalacic changes at the corresponding sites on late follow-up (► Fig. 78.4a–c). MR imaging is certainly the most sensitive technique for identifying small purulent collections adjacent to the skull and thus may be the technique of choice for monitoring response to antibiotic treatment.

78.2.7 Treatment

The primary treatment of intracranial suppuration of sinogenic or otogenic origin is antimicrobial.¹¹ The presence of subdural

or epidural pus is not by itself an indication for surgical drainage. Complete drainage of intracranial pus is not possible and is not necessary for cure. Indeed, in a recent cohort study based on a large administrative data set, more than 25% of patients with intracranial suppuration of sinogenic or otogenic origin were managed nonoperatively.⁶ The indications for surgical intervention are twofold: to obtain a microbiological diagnosis and to relieve symptomatic or threatening mass effect. The former indication often motivates urgent neurosurgical intervention at the time of presentation. The latter indication is clearly a matter for judgment based on careful assessment of the patient's clinical condition and imaging data. It may be present at

presentation, or it may arise at unpredictable times during the initial phase of treatment.⁵³ Surveillance imaging at frequent intervals allows close monitoring of the size and distribution of subdural collections.

A detailed discussion of antibiotic selection is beyond the scope of this chapter. In principle, therapy is guided by the sensitivities of the microbial isolates, but actual practice is not so intellectually satisfying. The administration of antibiotics before specimens can be obtained may compromise the sensitivity of culture methods. Although the concordance between intracranial cultures and sinus or ear cultures has been reported to be good,^{10,53,75} the relevance of extracranial cultures to intracranial suppuration is always uncertain, and the isolation of one organism does not eliminate the possibility of polymicrobial infection. Typically, three parenteral antibiotics must be employed at the outset to cover staphylococci, streptococci, gram-negative organisms, and anaerobes, and regardless of culture results, most patients are subjected to 6 weeks of broad-spectrum therapy.

Questions of surgical technique have been the topic of animated discussion in the literature, particularly for subdural empyema. Because surgery commonly must be undertaken on an urgent basis at odd hours, circumstances may favor the speed and simplicity of bur holes, and surgeons who feel compelled to discard craniotomy flaps elevated in the presence of pus naturally reserve craniotomy for patients who fail to respond to more limited interventions.⁵¹ This concern is misplaced. Craniotomy flaps elevated with an osteoplastic technique are highly resistant to infection, and under contemporary broad-spectrum antibiotic coverage, even free flaps heal reliably without complications.⁷⁶ On the other hand, many authorities have commented that patients treated initially with bur holes are subject to more frequent returns to the operating room for recurrent or new purulent collections than patients treated initially by craniotomy.^{1,8,13,16,77,78} In the very large case series of Nathoo and associates, craniotomy was associated with improved outcomes as well.¹ Craniotomy at presentation is the senior author's usual practice—an osteoplastic frontoparietotemporal craniotomy large enough for wide exposure of the more involved convexity and cautious drainage of the interhemispheric fissure, if necessary. And whatever may be the first intervention, reoperation for the reaccumulation of pus is so frequently necessary that this contingency must be born in mind in planning the initial exposure. Reoperation rates between 9 and 50% have been reported.^{1,5,8,77}

Subdural empyema of the posterior fossa is often diffusely distributed over the tentorial, petrosal, and occipital surfaces of the cerebellum, so a wide exposure is required.¹² Transient swelling of the cerebellum may necessitate leaving the craniotomy flap out and the dura unclosed. The senior author's usual practice in midline exposure of the posterior fossa is to leave a myofascial cuff along the nuchal line to permit reattachment of the cervical muscles to the occipital bone in the closure. This maneuver minimizes deformity and may reduce the risk for CSF-wound fistula when the dura must be left open in a large craniectomy defect. Posterior fossa subdural empyema is often complicated by hydrocephalus, which may be transient or persistent.¹⁰ In the large case series of Nathoo and associates, hydrocephalus developed in 77% of cases.¹²

External ventricular drainage is required in the acute phase, and a CSF shunt may be considered after the infection has been eradicated.

Surgery for epidural abscess differs in some respects. If a microbiological diagnosis has been obtained from sinus cultures, small collections may be managed nonoperatively.⁴⁶ Epidural abscesses are generally more focal than subdural empyemas, so drainage by bur holes often suffices.² Because most epidural abscesses are frontal, cosmetic considerations are pertinent. A bicoronal scalp incision for the drainage of frontal epidural collections can sometimes be avoided by employing an infraciliary incision and a small bur hole in the orbital roof to gain access to the anterior fossa directly or through the frontal sinus (► Fig. 78.5). The special case of Pott's puffy tumor raises the question of how to manage the associated osteomyelitis of the frontal bone. In the absence of a frank sequestrum, surgical restraint is in order. Craniectomy of the involved bone creates a skull defect with appalling cosmetic consequences and is generally unnecessary. Even a badly eroded frontal bone has the potential to heal solidly with a long course of antibiotic therapy (► Fig. 78.6a–d).

Most patients with sinogenic or otogenic intracranial suppuration require functional endoscopic sinus surgery or mastoidectomy at some point in time. There are no precise guidelines for whether and when these interventions may be indicated, so active communication with the consulting otolaryngologist is necessary. Coordinated drainage of intracranial and extracranial pus at the time of presentation has been advocated to minimize the risks for reaccumulation and antibiotic resistance,^{1,5,13,22,32} but controlled data are lacking.

The management of intracranial hypertension associated with subdural empyema has received little attention in the literature. Intracranial hypertension may be caused by the mass effect of the purulent collection itself, by hydrocephalus, or by cerebral venous thrombosis or dural sinus thrombosis. So far as possible, if a specific cause can be identified, it must be treated on its own terms. In the senior author's practice, the treatment of elevated intracranial pressure as a therapeutic goal in its own right proceeds by analogy with the management of severe traumatic brain injury. If the patient declines to a Glasgow Coma Scale score of 8 or less, intubation for controlled ventilation is undertaken, and intracranial pressure monitoring is indicated. Intracranial hypertension is managed by sedation, ventricular CSF drainage, and osmotic therapy with mannitol or hypertonic saline. If these measures do not suffice, lumbar CSF drainage, decompressive craniectomy, or barbiturate coma may be considered, just as for traumatic brain injury. Aggressive therapy is warranted. Although coma at presentation is a bad prognostic sign, patients who lapse into coma during treatment often make good recoveries.

Dogmatic guidance about the management of craniectomy flaps and skull defects after decompressive craniectomy in the clinical setting of suppuration is unwise, except to say that frankly osteomyelitic bone must be discarded. Craniectomy flaps in good condition may be frozen, if reliable local facilities are available, or stored in the subcutaneous tissues of the abdominal wall for later reconstruction. An interval of 3 to 6 months from the conclusion of antibiotic therapy is customary. Rates of recurrent infection after cranioplasty with stored bone in this clinical context are poorly defined.

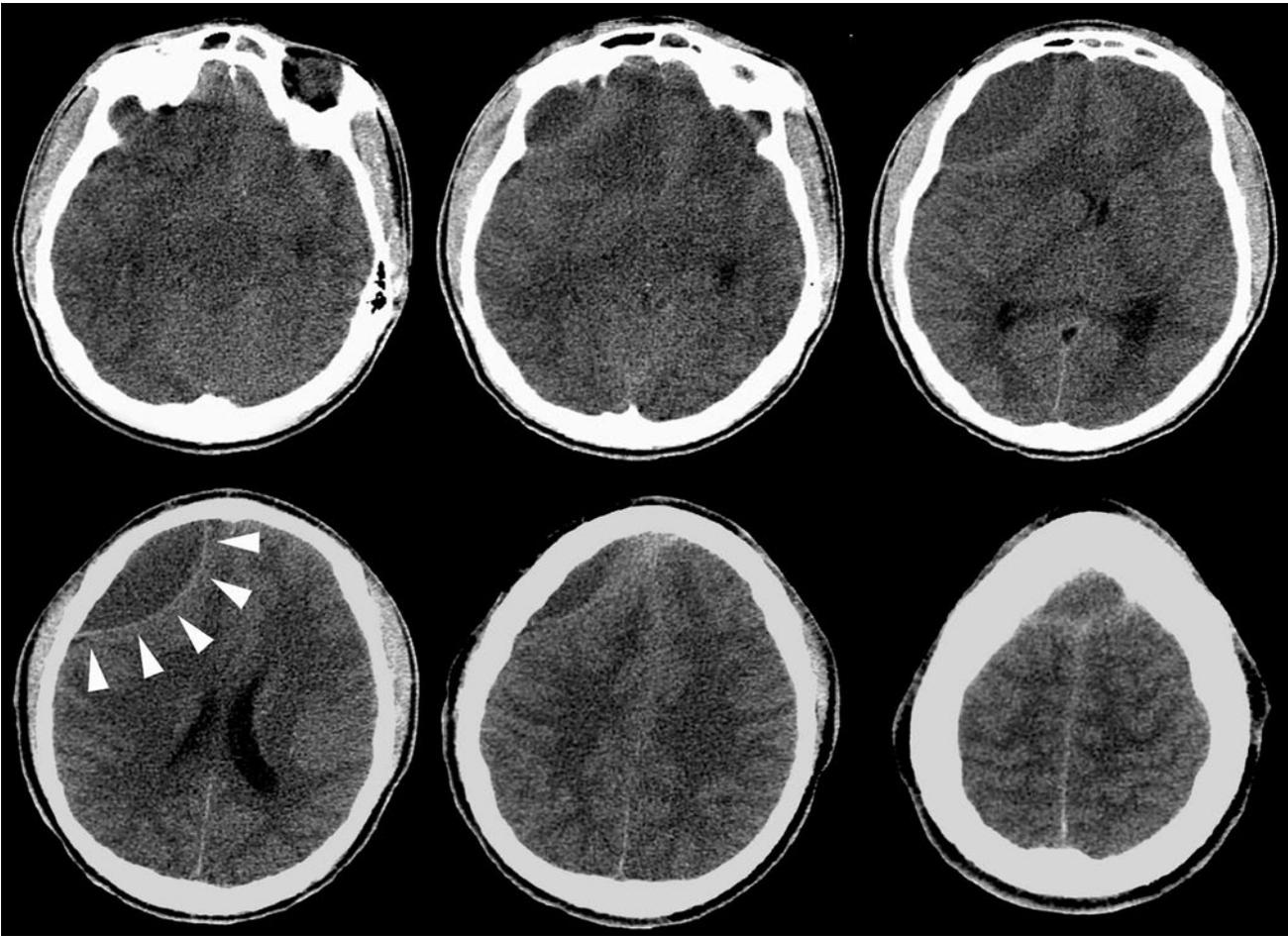


Fig. 78.5 This computed tomographic scan of the brain without enhancement shows a large anterior fossa epidural abscess. White arrowheads mark the biconcave contour. This collection was drained successfully through an infraorbital incision and a bur hole in the right orbital roof.

Seizures are a common complication of subdural empyema. A short course of prophylactic antiepileptic drug treatment is reasonable through the acute phase of the illness, by analogy with the management of severe traumatic brain injury. If actual seizures occur, the administration of antiepileptic drugs with maintenance of therapeutic blood levels under the supervision of a neurologist is appropriate.

Cerebral venous thrombosis and dural sinus thrombosis may complicate subdural empyema of sinogenic or otogenic origin. Focal thrombosis of the cerebral veins can in principle lead to venous infarction. This process was described clearly in the older autopsy literature,^{7,79} but it is seldom identified in contemporary clinical practice. If the thrombosis obstructs drainage through the sagittal or the dominant transverse or sigmoid sinus, it can cause diffuse cerebral venous congestion with a pseudotumor syndrome and intracranial hypertension. The most familiar clinical setting is sigmoid sinus thrombosis adjacent to an otitis or mastoiditis, and the consequent headaches, papilledema, and elevated opening pressure on lumbar puncture have been assigned the moniker “otitic hydrocephalus.”⁸⁰ The classic description of septic cavernous sinus thrombosis complicating acute sinusitis includes chemosis and proptosis from orbital venous congestion, ophthalmoplegia, visual loss due to retinal ischemia, and contralateral hemiplegia due to

thrombosis of the cavernous carotid artery. Fortunately, this entity is seen rarely, and even in the era before antibiotics its presentation was more commonly in fragments than in this fully elaborated picture.⁸¹ Septic thrombosis of the sigmoid or cavernous sinuses can extend into the internal jugular vein and generate septic embolization of the pulmonary circulation; this dangerous complication carries the eponym “Lemierre syndrome.”⁸² Dural sinus thrombosis can be demonstrated relatively readily by MR venography. Treatment measures include hydration, anticoagulation, surgical aspiration, and thrombectomy. For highly focal thromboses, endovascular thrombolysis may be considered, although the literature provides no guidance. Care must be exercised in balancing the clinical need against the risk for hemorrhagic complications, particularly in the context of recent or anticipated intracranial surgery.

78.2.8 Outcomes

Over time, the care of children with sinogenic and otogenic intracranial suppuration has been transformed by several readily identifiable advances. Before the introduction of antibiotics, subdural empyema was a uniformly fatal disease. With the appearance of penicillin and the sulfonamides, survival rates in

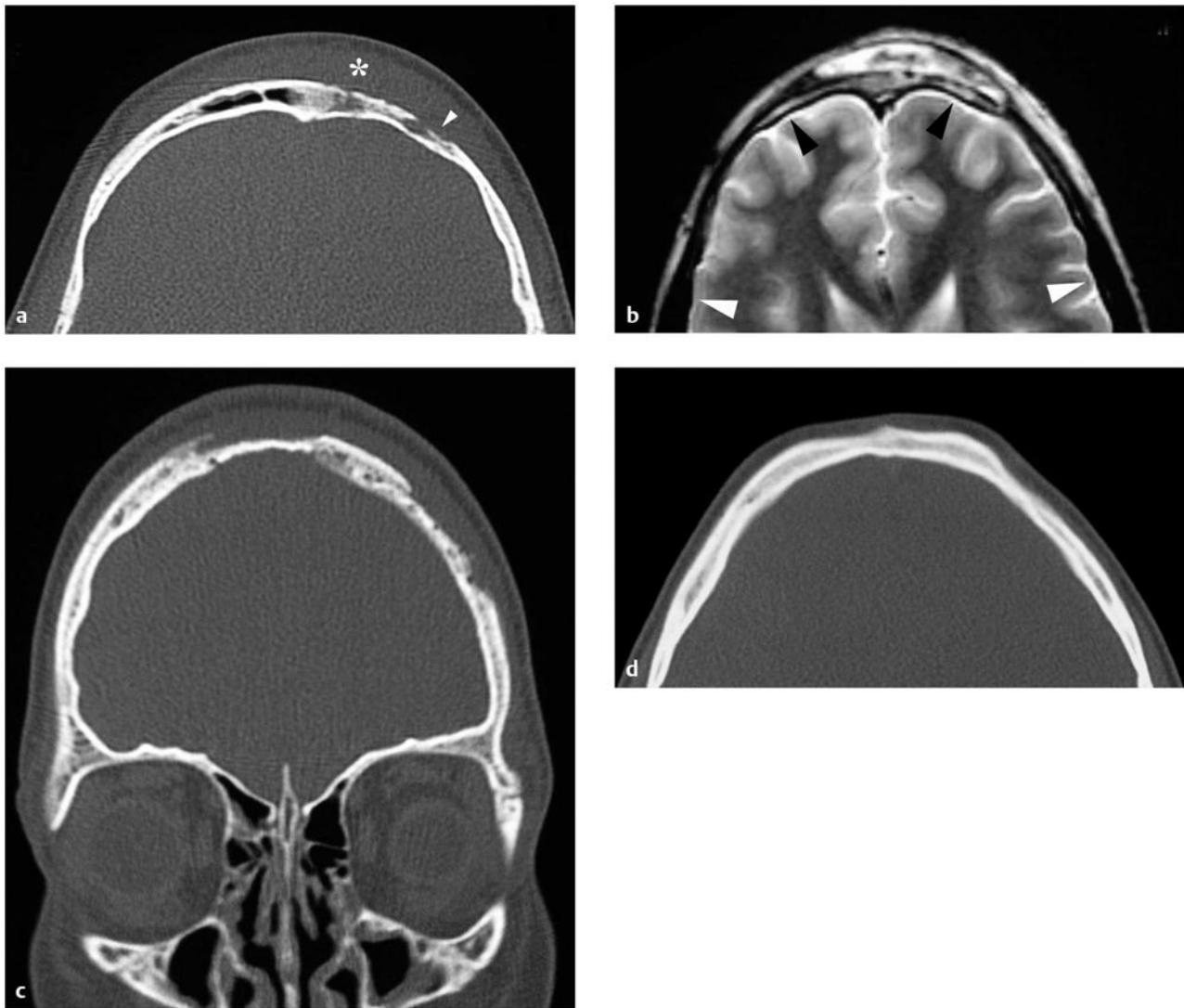


Fig. 78.6 (a) A male teenager came to attention with headache, fever, and extensive swelling of his forehead and scalp. This computed tomographic (CT) scan performed early in his course shows a large subperiosteal abscess (*white asterisk*) and osteomyelitis of the frontal bone with extensive erosive changes (*white arrowhead*). (b) This axial, T2-weighted MR imaging sequence shows high signal intensity, reflecting marrow edema in the involved frontal bone (*black arrowheads*), in comparison with the relatively uninvolved parietal bones (*white arrowheads*). There was no epidural abscess in this case. (c) Despite sinus drainage and parenteral antibiotics, the progress of the osteomyelitis was not arrested immediately. This coronal CT scan performed in the second week of treatment shows worsening erosion of the frontal bone. Extensive débridement of the frontal bone was considered, but it was deferred. (d) After 6 weeks of parenteral antibiotic therapy, the frontal bone healed. (Courtesy of Drs. Joseph Piatt, Jennifer Smith, and Eric Faerber.)

the neighborhood of 50% or better became possible.^{17,34,77,83,84} The development of computed brain imaging has simplified the diagnosis greatly, and its liberal employment in the course of treatment has facilitated not only prompt intervention for complications but also confident observation of stable or resolving collections. Concurrently, the introduction of third-generation cephalosporins, metronidazole, vancomycin, sulbactam, meropenem, and other advanced antibiotics has augmented the power of medical therapy. Contemporary mortality rates for subdural empyema are reported between 13% and nil,^{1,1.5,8-11,16,20,22,23,28,51,53} and there is now an expectation that isolated epidural abscess can be treated without mortality.^{2,8,9,22} Coma at presentation remains a grave

prognostic sign, but patients presenting with hemiparesis or other focal neurologic signs often make gratifying recoveries with little or no long-term disability.^{1,5,9,11,16,22,28,77}

78.2.9 Prevention

Because sinusitis, otitis, and mastoiditis are so common and commonly run such benign courses, and because their intracranial complications are so infrequent and threatening, there has been much bootless discussion about preventative measures. Intracranial suppuration has been blamed on delayed recognition of the preceding infection, inadequate treatment, delayed treatment, and poor compliance with

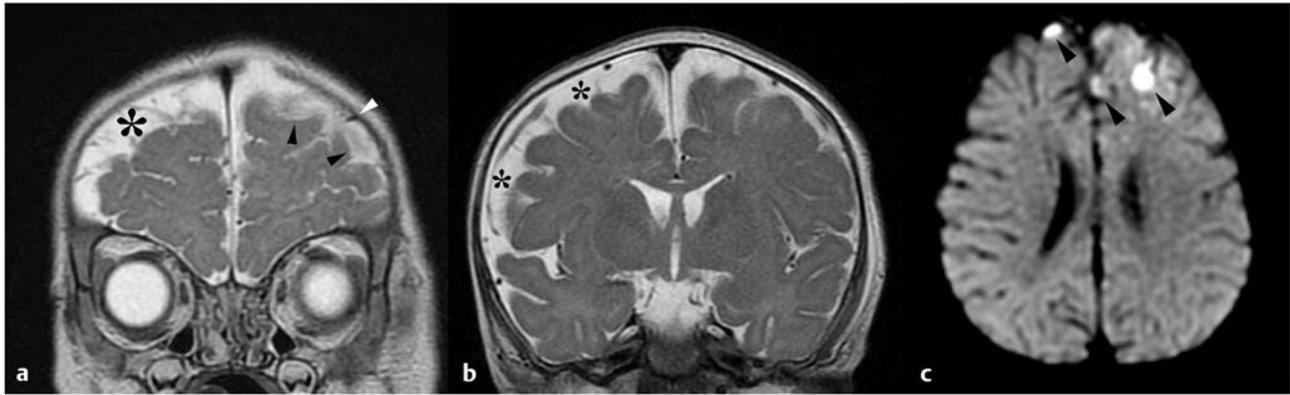


Fig. 78.7 (a) A 6-month-old infant developed pneumococcal meningitis. Coronal T2-weighted magnetic resonance imaging shows prominence of the subarachnoid spaces (black asterisks). Over the left frontal convexity is an extracerebral collection with intensity slightly lower than that of cerebrospinal fluid (black arrowheads). This collection is confirmed to be in the subarachnoid space by the presence of a vascular flow void (white arrowhead) within it. (b) Diffusion-weighted imaging sequence from the same study shows droplets of high-signal pus lying in a sulcus and (c) on the surface of several gyri (black arrowheads).

treatment.^{11,18,28} Although these factors may seem to contribute to individual anecdotal cases, systematic analysis is impossible. The degree to which these same factors are present in the overwhelmingly more numerous cases of predisposing head infections that do not progress to intracranial complications is unknowable. Numerous international authorities have developed guidelines for the management of bacterial sinusitis and otitis, but the prevention of complicating intracranial suppuration has fallen outside the scope of these efforts.^{85–88}

78.3 Meningitis

Subdural empyema complicating meningitis in infants and young children is much less common in contemporary North American practice than it was in the past century, before the adoption of universal immunization against *Haemophilus influenzae* and *Streptococcus pneumoniae*. Over time, as the incidence of this condition has plummeted, technological advances have transformed the simplicity and sensitivity of diagnostic methods. For this reason, most of the literature is either old or international, and its lessons require judicious application.

78.3.1 Pathology

Several distinct types of extracerebral collection can complicate the course of young children undergoing treatment for bacterial meningitis. In addition to subdural purulence indistinguishable from sinogenic subdural empyema, watery hypocellular fluid can collect in the subdural space—so-called subdural effusion. Meningitic subdural empyema can also be confused with focal collections of thick pus in the subarachnoid space. Distinction among these entities has obvious surgical implications: an effusion can be drained through a needle. Subdural empyema requires bur hole drainage or craniotomy. And there is no practical, safe technique for the drainage of subarachnoid pus. As will be seen, these entities can be distinguished with modern imaging methods.

78.3.2 Microbiology

As the population-based incidence of meningitis due to *H. influenzae* and *S. pneumoniae* has fallen, other organisms have accounted for larger fractions of cases of meningitic extracerebral collections—notably group B streptococci, enteric gram-negative organisms, and *Neisseria meningitidis*.^{8,37,89}

78.3.3 Clinical Presentation

Even among young children, the development of meningitic subdural collections seems to be a function of age; in one large case series that predated computed brain imaging, the prevalence ranged from 21% among infants younger than 6 months to only 2.6% in children in the second year of life. No collections were detected in older children.^{18,90} Meningitic extracerebral collections are seldom recognized at the time of diagnosis of the underlying meningitis; they are later-developing complications. The typical clinical presentation is recurrent or persistent fever or seizures in an infant or young child who seemed otherwise to have had a satisfactory initial response to antibiotic therapy.⁹¹ In one study, the prevalence rates of subdural empyema among infants with persisting fever at 9 days and in those with recurrent fever were 27% and 23%, respectively.⁹¹ In the era after antibiotics but before immunization and computed imaging, when this complication was more common, new focal neurologic deficits, depressed responsiveness declining to coma, and opisthotonus were described as well, but in that era, diagnosis was by subdural puncture. Such catastrophic presentations are unusual now.

78.3.4 Imaging

The imaging characteristics of meningitic subdural empyema generally conform to the descriptions of sinogenic and otogenic collections. On MR imaging, DWI sequences are especially sensitive. MR imaging also permits the distinction between purulent subdural collections and pus in the subarachnoid space itself. In the subarachnoid space, pus may appear as high-signal

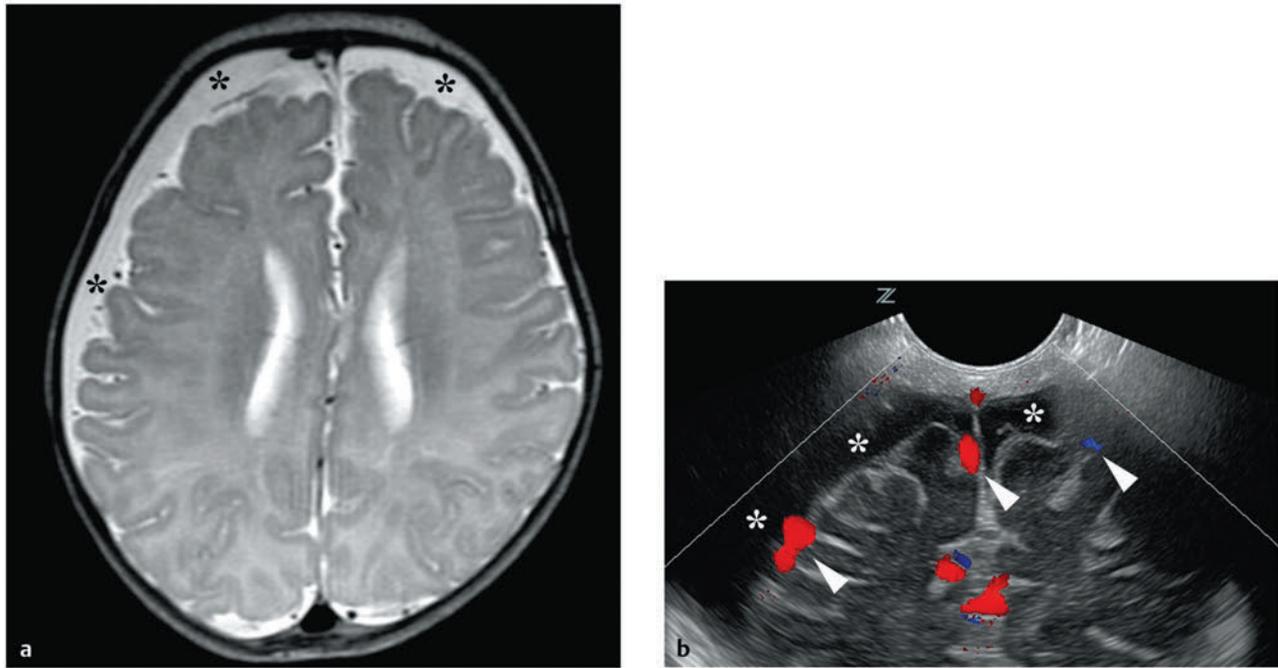


Fig. 78.8 (a) An infant with group B streptococcal meningitis underwent magnetic resonance imaging. This axial T2-weighted image shows bilateral subdural effusions (*black asterisks*). The subdural collections are homogeneous, with signal intensity close to that of cerebrospinal fluid. (b) Ultrasound examination of the brain of the same patient shows hypoechoic extracerebral collections (*white asterisks*), confirmed to be subdural by the close apposition to the cortical surface of the Doppler signals (*white arrowheads*) corresponding to vessels in the subarachnoid space.

droplets or as a laminar collection adherent to the surface of the brain (► Fig. 78.7a,b).⁹² Pus imaged in the subarachnoid space may have an internal structure produced by vascular flow voids, whereas subdural pus has homogeneous signal characteristics only sometimes interrupted by reactive, enhancing membranes. The signal characteristics of subdural effusions are close to those of water, and by definition effusions do not restrict diffusion.⁷¹

Among infants with open fontanels, ultrasound may be useful to distinguish reactive subdural effusions from empyema and empyema from subarachnoid pus.⁹³ Whether it is in the subdural space or in the subarachnoid space, pus is hyperechoic. In the subarachnoid space, echogenic inflammatory changes conform to the surface of the brain and fill the sulci. Subdural collections can be distinguished from the subarachnoid space by the additional presence in the latter of vascular Doppler signals (► Fig. 78.8a,b). Subdural effusions are hypo- or anechoic with floating particulate debris.

78.3.5 Treatment

The treatment of meningitic extracerebral suppuration has undergone a notable evolution over the history of the subspecialty of pediatric neurosurgery. McKay et al advocated craniotomy not only for the drainage of pus but more importantly for the stripping of inflammatory membranes off the pial surface of the brain.⁹⁴ They believed that the continuing presence of inflammatory membranes promoted the reaccumulation of pus and restricted subsequent growth of the brain. This dogma, which applied to chronic subdural hematoma as well as to

subdural empyema, was eventually overthrown by Shulman and Ransohoff, Collins and Pucci, Goodman and Mealey, and other worthies of the next generation, who observed that the natural history of subdural membranes is to disappear.^{95–97} Less radical interventions, including the novel pleural shunt, seemed to yield satisfactory outcomes.^{95,98,99} Nevertheless, diagnostic vigilance and assiduous drainage of all detectable subdural pus continued to be the guiding principles.

What has enabled the adoption of a more expectant approach has been the development and ready availability of computed imaging. Contemporary brain imaging gives the surgeon comprehensive data on the volume, distribution, and temporal evolution of extracerebral suppuration, and experience has shown that most of these collections resolve without drainage. The treatment of meningitic extracerebral suppuration is primarily the antibiotic treatment of meningitis. The indications for surgical intervention are symptomatic intracranial hypertension, threatening mass effect, or expansion on sequential imaging despite appropriate antibiotic therapy. When compelling indications exist for the drainage of collections, a graduated approach is appropriate, beginning with subdural puncture or bur holes (► Fig. 78.9).¹¹ Craniotomy is not required as often as for older children with sinogenic or otogenic suppuration. Chronic collections with accelerated head growth and craniocerebral disproportion can be managed with pleural or peritoneal shunts, although the senior author has never encountered such circumstances.

The question may arise of continuing culture positivity of the extracerebral collection as a possible indication for surgical intervention. In reports before and after the introduction of

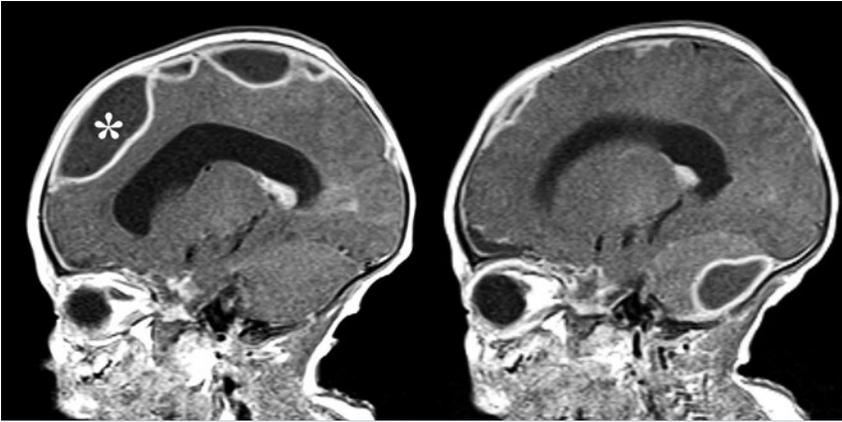


Fig. 78.9 This neonate developed subdural empyemas complicating *Escherichia coli* meningitis. The largest collection (white asterisk) was drained with a needle through the anterior fontanel. It was still culture-positive even though the cerebrospinal fluid (CSF) had been sterilized. Nevertheless, without any change in antibiotic therapy, after several weeks the other collections eventually resolved. The infant later required a CSF shunt for progressive hydrocephalus.

computed imaging, an offending organism was cultured from between 11 and 23% of subdural specimens.^{89,100–102} How this datum can affect treatment is a matter for discussion on a case-by-case basis. Regardless of culture results from a sample of subdural pus, patients who have had a complicated initial clinical course and have been recognized to have extracerebral collections are already committed to a longer course of antibiotic administration than the usual 10 to 14 days. Such patients can be managed safely by clinical observation and sequential imaging.

78.4 Trauma and Surgery

Extracerebral suppuration is very seldom encountered as a complication of elective surgery or surgery for trauma in pediatric practice. Aside from case reports, there is no literature devoted to the pediatric age group, and the largest series of cases of postsurgical and posttraumatic infection include very small numbers of children and fail to discuss them separately.^{62,103–105} Principles must be extrapolated from adult practice.

Risk factors are recognized: inadequate initial care of open traumatic wounds, multiplicity of previous craniotomies at the same site, previous surgery opening the facial sinuses, employment of synthetic dural substitutes or cranioplasty materials, previous radiation therapy, advanced age, and failure to administer prophylactic antibiotics.^{103–105}

The temporal course of infection varies. Subdural empyema and epidural abscess tend to present within a few weeks of the preceding operation. Osteomyelitis of the craniotomy flap—invariably associated with some degree of epidural pus—can appear after notoriously long latencies. Median times to the presentation of infections requiring surgical treatment have been reported in the neighborhood of 4 to 6 weeks.^{104,105}

In keeping with the hospital acquisition of infection, the predominant organisms are *Staphylococcus* species and gram-negative rods. As with sinogenic and otogenic suppuration, the possibility of polymicrobial infection must be considered, but anaerobes are less commonly encountered and tend to be gram-positive skin organisms, such as *Propionibacterium acnes* and diphtheroids.^{104–107}

Exploration of the wound is indicated. In this respect, postsurgical and posttraumatic infection differs from sinogenic, otogenic, and meningitic suppuration, for which closely observed medical management can be considered in selected cases. The collection must be cultured, and the wound must be débrided

of synthetic material and devitalized tissue. The disposition of the craniotomy flap itself is a matter for judgment. In cases of acute infection after a short latency, if osteomyelitis is not clearly established in the flap, it may be scrubbed with antibiotic or antiseptic solutions and replaced with reasonable hope of healing under the cover of a protracted course of parenteral and oral antibiotics.^{76,107} Salvage of frankly osteomyelitic craniotomy flaps by antibiotic wound irrigation has been described.^{106,108} Because living with a large skull defect is such an ordeal for most patients and families, strenuous efforts to preserve the craniotomy flap are appropriate. In large case series, more than one operation has been required in 44 to 55% of cases.^{103,104}

Controlled data are lacking, but when the treatment of postsurgical or posttraumatic infection has created a skull defect, deferral of cranioplasty for 3 to 6 months is common practice.¹¹

78.5 Conclusion

Although the presentation may be alarming, the attentive treatment of epidural abscess and subdural empyema yields good outcomes in the great majority of cases. These cases represent rewarding opportunities for application of the experience and skill of the neurosurgeon.

Pearls

- The primary indications for surgery are to obtain pus for microbiological diagnosis and to relieve threatening elevations of intracranial pressure.
- Frequent brain imaging early in the course of treatment is critical to monitor responses to antimicrobial therapy.
- Drainage must be undertaken for collections that enlarge during therapy.
- Surgical restraint is appropriate in the management of osteomyelitis of the skull in the setting of sinogenic or otogenic suppuration.

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79 Brain Abscess and Encephalitis

Jonathan Pindrik and Edward S. Ahn

79.1 Brain Abscess

79.1.1 Overview

Intraparenchymal abscesses require early diagnosis and intervention to minimize morbidity and mortality in the pediatric population. Because of the wide variety of potential pathogens, microbiological evidence through culture data provides a foundation for diagnosis and treatment. Appropriate therapy of intracranial abscesses requires combined surgical and medical management and collaborative care. This chapter highlights the main diagnostic considerations and treatment options for brain abscesses in the pediatric population.

79.1.2 History

William Macewen recorded the first diagnosis of a pediatric brain abscess in 1876 by postmortem examination.^{1,2} Clinical suspicion arose because of the patient's symptomatology, while localization stemmed from neurologic assessment. The surgical management of brain abscesses became more widely used in the 1930s, shortly after Walter Dandy recorded the first attempted aspiration of an intracranial abscess in 1926.² Subsequently, Pennybacker achieved the first safe and effective surgical resection of a cerebellar abscess in 1948.³

79.1.3 Epidemiology

Children age 4 to 7 years comprise the group of pediatric patients most commonly affected by brain abscesses.¹ Of all intraparenchymal abscesses, nearly 25% occur in the pediatric population younger than age 15.⁴ Despite a low incidence of 4 cases per million, intraparenchymal abscesses require close attention in the pediatric population because they carry high risks for morbidity and mortality.^{1,5}

79.1.4 Pathology

An abscess is a well-circumscribed, encapsulated collection of purulent material containing microorganisms, inflammatory cells, cellular debris, and necrotic material.^{2,6} Abscess formation within the brain parenchyma proceeds through four stages (see box "Stages of Brain Abscess Formation (p. 1036)"). The initial stage of early cerebritis involves minimal central necrosis and surrounding edema, with subtle radiographic features. Imaging characteristics become more noticeable during late cerebritis, with early discontinuous sparse enhancement. During this phase, inflammatory cells congregate circumferentially around a necrotic core. Subsequently, during early capsule formation, fibroblasts create a thin capsule that exhibits contrast enhancement on computed tomography (CT) and magnetic resonance (MR) imaging. The late capsule stage displays greater contrast enhancement along a thicker, vascular, and more fibrotic abscess wall that surrounds a necrotic core.¹

Stages of Brain Abscess Formation

- Stage I: Early cerebritis
 - Days 1–3
 - Small area of central necrosis
 - Surrounding edema
 - Head computed tomographic findings variable but typically not prominent; hypodensity or faint contrast enhancement possible
- Stage II: Late cerebritis
 - Days 4–9
 - Necrotic core
 - Surrounding inflammatory cells
 - Early patchy enhancement on imaging
 - Thicker rim of peripheral enhancement later on imaging
- Stage III: Early capsule formation
 - Days 10–14
 - Necrotic core
 - Thin capsule formed by fibroblasts
 - Distinct rim enhancement on imaging
- Stage IV: Late capsule stage
 - Day 15 and beyond
 - Necrotic core
 - Thicker vascular capsule with increased fibrosis
 - Thicker rim of peripheral enhancement on imaging

Source: Adapted from Frazier JL, Ahn ES, Jallo GI. Management of brain abscesses in children. *Neurosurg Focus* 2008;24(6):E8.¹

79.1.5 Pathophysiology

Various mechanisms and underlying conditions account for the occurrence of intracranial abscesses. Potential etiologies include seeding from penetrating trauma, local spread of a contiguous infection, hematogenous spread of a distant infection, predisposition due to congenital abnormalities, and complications of an intracranial procedure. Patient characteristics and environmental factors influence the specific mechanism of brain abscess formation. For instance, neonates and infants display higher rates of cerebral abscess formation due to hematogenous dissemination and bacterial meningitis.¹ In developing nations, the contiguous spread of suppurative otitis media is a predominant cause of intraparenchymal abscesses.^{1,2,7}

Contiguous Spread

The intracranial spread of nearby infections typically occurs through necrotic tissue or focal areas of osteomyelitis.⁵ For instance, contiguous spread via the labyrinthine system or tegmen tympani may account for temporal or cerebellar abscesses resulting from mastoiditis or otitis media.¹ Contiguous spread of infection may also occur through the vasculature. Small, valveless diploic veins traverse the sinus walls and communicate with the dural venous plexuses, offering routes of entry for

Table 79.1 Common characteristics of pediatric brain abscesses based on predisposing condition and mechanism of infection

Predisposing condition	Mechanism of infection	Typical abscess location	Common microorganisms
Penetrating head trauma	Direct inoculation	Any intraparenchymal site	<i>Staphylococcus aureus</i> , viridans streptococci, <i>Streptococcus pneumoniae</i> , Enterobacteriaceae
Prolonged bacteremia, endocarditis	Hematogenous spread (remote location)	Arterial distribution, especially middle cerebral artery territory	<i>S. aureus</i> , streptococci
Sinus or dental infection	Contiguous spread Local venous spread	Frontal lobes	Gram-positive cocci and gram-negative bacilli; streptococci (e.g., <i>Streptococcus milleri</i>), <i>S. aureus</i> , Enterobacteriaceae
Chronic otitis media or mastoiditis	Contiguous spread	Temporal lobes, cerebellum	Gram-negative bacilli, streptococci (aerobic and anaerobic), Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>S. aureus</i>
Congenital cyanotic heart disease	Right-to-left shunting, paradoxical emboli	Arterial distribution, especially middle cerebral artery territory	Gram-positive cocci, viridans streptococci
Immunocompromised status	Opportunistic infections	Arterial distribution, any intraparenchymal site	Fungi, yeast: <i>Candida</i> , <i>Aspergillus</i> , Mucorales
Immunodeficient status (AIDS)	Opportunistic infections	Any intraparenchymal site	<i>Toxoplasma gondii</i> , <i>Nocardia</i> , <i>Mycobacterium</i>
Ventriculoperitoneal shunt	Foreign body, ascending infection	Along proximal catheter trajectory; may include ventriculitis	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , gram-negative bacilli, <i>P. aeruginosa</i>

infections involving the paranasal sinuses.⁵ Local infections predisposing to intraparenchymal abscesses include otic, dental, sinus, facial, and periorbital infections.

Predisposing Conditions

Several predisposing conditions in children relate directly to the mechanisms of intracranial infection (► Table 79.1). Congenital cardiac disease is an underlying abnormality in nearly 30% of children with intraparenchymal abscesses.¹ Cardiac anomalies include tetralogy of Fallot, transposition of the great vessels, atrial or ventricular septal defects, and Eisenmenger syndrome. The right-to-left shunt created in cyanotic heart disease allows the passage of paradoxical emboli and intracranial seeding via hematogenous spread.^{1,4,6} Immunosuppression is another important predisposing factor for brain abscess formation. Incompetence of the immune system occurs in the setting of immunosuppression for organ transplant, chemotherapy for malignancy, or underlying diseases like acquired immunodeficiency syndrome (AIDS). Pulmonary conditions, including cystic fibrosis and bronchiectasis, increase the risk for respiratory infections that may lead to brain abscess formation. Intracranial abscesses may also arise because of congenital abnormalities like dermoid cysts and dermal sinus tracts, which allow the direct invasion of microorganisms.^{8,9}

Trauma and Foreign Bodies

Penetrating trauma is a common cause of pediatric intracranial infection due to retained foreign debris or skull fragments. Often planted deep within the brain, such material cannot be

removed safely and serves as a nidus for infection.¹ Up to 13% of brain abscesses result from penetrating craniofacial trauma. Conversely, in from 5 to 16% of cases, penetrating head trauma leads to intraparenchymal abscess formation.¹ Other intracranial foreign bodies, such as ventricular shunts for hydrocephalus, also predispose to abscess formation. Microorganisms may colonize an intracranial catheter or ascend a distal catheter from the peritoneal space. Despite these plausible mechanisms, intraparenchymal abscesses associated with ventricular shunts occur infrequently.¹⁰ Although various mechanisms and predisposing conditions have been described, nearly 30% of intraparenchymal abscesses occur without an identified etiology.^{1,4}

Abscess Location

The specific location of an intraparenchymal abscess may reflect the mechanism of disease spread (► Table 79.1). For instance, abscesses in the distribution of the intracranial arterial circulation, especially the middle cerebral artery (MCA), suggest hematogenous dissemination from a remote source.^{4,6} Local venous drainage of sinus, dental, or facial infections into the cavernous sinus may lead to frontal lobe abscesses via retrograde thrombophlebitis.¹ Additionally, frontal abscesses may arise from dental or sinus infections via contiguous spread.^{4,6} Temporal lobe or cerebellar abscesses may suggest direct invasion from mastoiditis or chronic middle ear infections.⁴⁻⁶ Infratentorial abscesses may result from infection of posterior fossa dermoid cysts and associated dermal sinus tracts.^{3,8} The locations of intraparenchymal abscesses also correlate with age. Younger patients have higher rates of cerebellar abscesses, whereas older children have a higher incidence of temporal lobe abscesses.⁶

79.1.6 Microbiology

The specific type of infecting microorganism depends on patient characteristics and mechanism of disease (► Table 79.2). Gram-positive cocci, including *Streptococcus* and *Staphylococcus* species, are the most common group of microorganisms found in pediatric brain abscesses.^{1,2,6} Gram-negative rods, including the Enterobacteriaceae family and *Haemophilus* species, are the next most common group of pathogens implicated. Facultative and obligate anaerobic organisms are the predominant isolates reported in intracranial abscesses historically.⁵

Subpopulations of children exhibit trends with respect to infecting microorganisms. For instance, immunocompromised children show a higher frequency of intraparenchymal abscesses infected with fungi, yeast, *Nocardia*, *Toxoplasma gondii*, and *Mycobacterium tuberculosis*.^{4,5} The rising prevalence of these infections results from increasing rates of AIDS, chemotherapy, and immunosuppression.² In the neonatal population, *Citrobacter* is the most common cause of brain abscesses, especially in the setting of meningitis.^{1,6} Intraparenchymal abscesses associated with cyanotic congenital heart disease tend to be infected with viridans streptococci and other gram-positive cocci.⁵ Similarly, intracranial penetrating trauma predisposes to brain abscesses infected with *Staphylococcus aureus*, viridans streptococci, and *Streptococcus pneumoniae*.⁵ Intraparenchymal abscesses associated with ventriculoperitoneal shunts frequently exhibit culture isolates of *S. aureus* and *Staphylococcus epidermidis*, enteric gram-negative bacilli, and *Pseudomonas aeruginosa*.⁵ Delayed abscesses with *Propionibacterium acnes* may form along a retained ventricular catheter.¹¹ Multiple organisms may be present in up to 30% of brain abscesses; alternatively, many abscesses lack remarkable culture results.⁴

79.1.7 Clinical Presentation

Generalized Findings

Children with brain abscesses often present with symptoms related to infection and elevated intracranial pressure (ICP). Although common, the classic triad of fever, headache, and focal neurologic deficit is not present in the majority of patients.^{4,12} Up to 70% of children with an intraparenchymal abscess present with fever.^{1,4} Furthermore, most pediatric patients with an intraparenchymal abscess present with at least one symptom or sign of elevated ICP, including headaches, emesis, and papilloedema.⁴ Neonates with elevated ICP may show fullness or bulging of the anterior fontanel and increasing head circumference.⁶

A patient's neurologic status may be subtle confusion, lethargy, stupor, or coma depending upon the time of presentation and fulminance of disease.⁶ Coexistent meningitis may contribute to a declining neurologic status.³ Any acute decrement in the examination findings or Glasgow Coma Scale score can signify intraventricular extension of the abscess contents, a highly morbid and potentially fatal occurrence.^{1,6}

Neurologic Deficits

As with most intracranial lesions, the location, size, and surrounding edema of a brain abscess dictate the neurologic findings. Focal neurologic signs or seizures occur in 25 to 50% of pediatric patients with brain abscesses.⁴ Seizures are a

presenting symptom in nearly 27% of children with intraparenchymal abscesses.² Frontal lobe lesions often lead to personality or behavioral changes, difficulty with cognitive processes, or disinhibition.⁶ Additionally, contralateral motor weakness may develop from mass effect on the motor cortex. Cerebellar lesions may produce gait or limb ataxias, incoordination, eye movement abnormalities, or symptoms of elevated ICP due to obstructive hydrocephalus. Abscesses within the brainstem can cause cranial nerve deficits (cranial nerves III, VI, and VII) or upper motor tract signs.¹³

Parietal and temporal lobe abscesses cause deficits depending upon laterality and the structures involved. Nondominant parietal lesions may lead to contralateral hemineglect, dyspraxia, and visual field cuts. Abscesses in the parietal lobe of the dominant hemisphere may cause subtle dysphasias and visual field cuts as well. Visual deficits resulting from parietal lesions range from contralateral inferior quadrantanopsia to homonymous hemianopia depending upon involvement of the optic radiations.⁶ Temporal lobe abscesses may also cause visual field cuts. Additionally, abscesses within the temporal region of the dominant hemisphere may lead to pronounced aphasia.

79.1.8 Diagnosis

Imaging Findings

CT and MR imaging of the head have significantly improved the early diagnosis of brain abscesses. Ultrasonography of the head can also be used intraoperatively or in infants with open fontanelles. With greater speed and ease of acquisition than MR imaging, CT of the head typically portrays a centrally hypodense lesion with a peripheral rim of contrast enhancement.² Surrounding hypodensity typically indicates vasogenic edema (► Fig. 79.1). The findings on CT of the head may lag the clinical presentation; therefore, a lack of noteworthy findings should not exclude the diagnosis of brain abscess initially.⁴

Offering greater anatomical detail, MR imaging provides a better characterization of abscess size, location, quantity, and relation to neighboring structures.⁶ T2-weighted sequences depict a centrally hyperintense lesion with a hypointense rim and surrounding increased signal, consistent with vasogenic edema (► Fig. 79.2). Gadolinium administration on T1-weighted imaging portrays a centrally hypointense lesion with a peripheral rim of contrast enhancement (► Fig. 79.3). MR imaging also offers enhanced visualization of satellite lesions, cerebritis, and the differentiation between edema and liquefactive necrosis.¹ The MR imaging characteristics of an intraparenchymal abscess mirror those of other intracranial lesions in a child; the differential diagnosis broadly includes tumor, tuberculoma, cysticercosis, and vascular lesions.¹

Specialized MR imaging sequences allow further differentiation between brain abscesses and similarly appearing lesions. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping help distinguish brain abscesses from cystic or necrotic tumors. A purulent abscess cavity typically exhibits high signal intensity on DWI but hypoattenuation on ADC mapping, consistent with diffusion restriction (► Fig. 79.4 and ► Fig. 79.5).^{14,15} In contrast, the cystic or necrotic portions of brain tumors typically appear hypointense on DWI with elevated ADC values. Exceptions to the DWI and ADC patterns may

Table 79.2 Microorganisms isolated in pediatric brain abscesses

Domain	Microbiological descriptors	Genus and species	Common patient characteristics	Additional comments
Bacteria	Aerobic and facultatively anaerobic, gram-positive cocci	<i>Streptococcus pneumoniae</i>	Meningitis, head trauma	
		Viridans streptococci	Cyanotic congenital heart disease, head trauma	
		<i>Streptococcus milleri</i> group	Child beyond neonatal period	Subgroup of viridans streptococci, also referred to as <i>Streptococcus anginosus</i> ; microaerophilic
		<i>Staphylococcus aureus</i>	Head trauma, sinusitis, ventricular shunt, chronic otitis media	Increasing prevalence of methicillin-resistant <i>S. aureus</i> (MRSA)
		<i>Staphylococcus epidermidis</i>	Ventricular shunt	Create biofilms adherent to catheters
	Facultatively anaerobic, gram-positive bacilli	<i>Listeria monocytogenes</i>	Immunocompromised host, neonate	Sensitive to ampicillin
	Aerobic, gram-positive bacilli	<i>Nocardia</i> species	Immunocompromised host, AIDS	Often confused with tuberculosis because of acid-fast staining and filamentous structure
	Facultatively anaerobic, gram-negative bacilli; Enterobacteriaceae family	<i>Escherichia coli</i>	Ventriculoperitoneal shunt	Sensitive to third-generation cephalosporins
		<i>Klebsiella</i> species	Ventriculoperitoneal shunt	Sensitive to third-generation cephalosporins
		<i>Proteus</i> species	Ventriculoperitoneal shunt, otic infection	Sensitive to third-generation cephalosporins
		<i>Enterobacter</i> species	Ventriculoperitoneal shunt, otic infection	Sensitive to fourth-generation cephalosporins
		<i>Citrobacter</i> species	Neonate, infant; meningitis	Most common microorganisms in neonatal brain abscesses
	Anaerobic, gram-negative bacilli	<i>Bacteroides</i> species	Chronic otitis media, mastoiditis, sinusitis	Most common anaerobic organisms found in temporal lobe abscesses due to otic infection
	Aerobic, gram-negative bacilli	<i>Pseudomonas aeruginosa</i>	Ventriculoperitoneal shunt, chronic otitis	Also present in immunodeficient hosts
	Aerobic and facultatively anaerobic, gram-negative bacilli	<i>Haemophilus influenzae</i>	Meningitis, chronic sinusitis	Sensitive to third-generation cephalosporins
	Aerobic, acid-fast bacilli	<i>Mycobacterium tuberculosis</i>	Immunodeficient host, AIDS	
Fungi	Branching pattern of septate hyphae	<i>Aspergillus</i>	Immunocompromised host	Typically spread from paranasal sinusitis or respiratory infections
	Dimorphic mycelial and yeast forms	<i>Coccidioides immitis</i>	Immunocompromised host	Geographic predominance in southwestern United States, Central and South America
	Budding yeast	<i>Cryptococcus neoformans</i>	Immunodeficient host, AIDS	Sensitive to amphotericin B and flucytosine
Protozoa	Infectious cyst form	<i>Toxoplasma gondii</i>	Immunodeficient host, AIDS	Increasing prevalence in regions where AIDS is endemic
	Trophozoite and cyst forms	<i>Entamoeba histolytica</i>	Developing nations, immigrants to United States	Sensitive to metronidazole

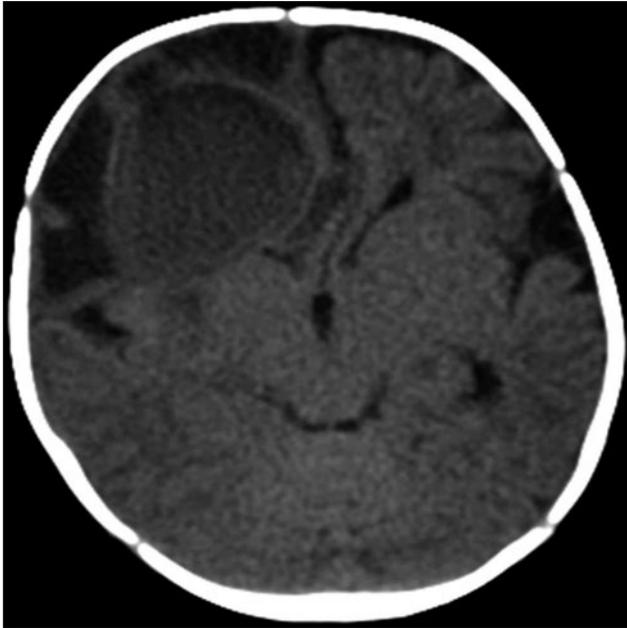


Fig. 79.1 Axial computed tomographic scan of the head (without contrast) showing a right frontal brain abscess with surrounding hypodensity anteriorly and laterally, consistent with vasogenic edema.

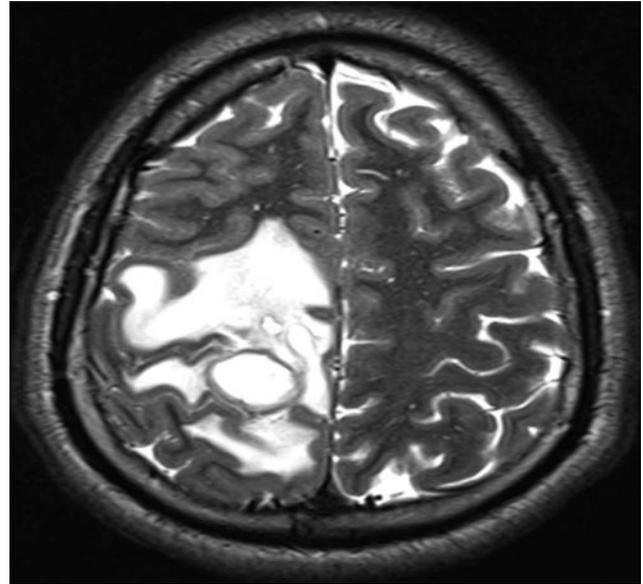


Fig. 79.2 Axial T2-weighted magnetic resonance imaging sequence depicting a right parietal intraparenchymal abscess with surrounding hyperintense vasogenic edema.

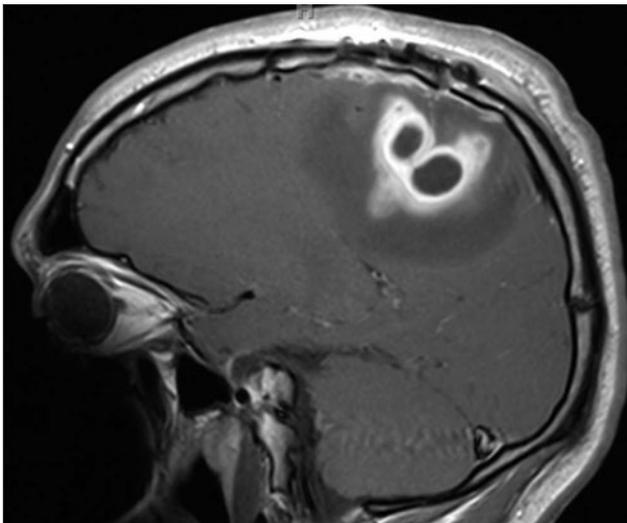


Fig. 79.3 Sagittal T1-weighted magnetic resonance imaging sequence with gadolinium administration showing peripheral contrast enhancement surrounding a hypointense core.

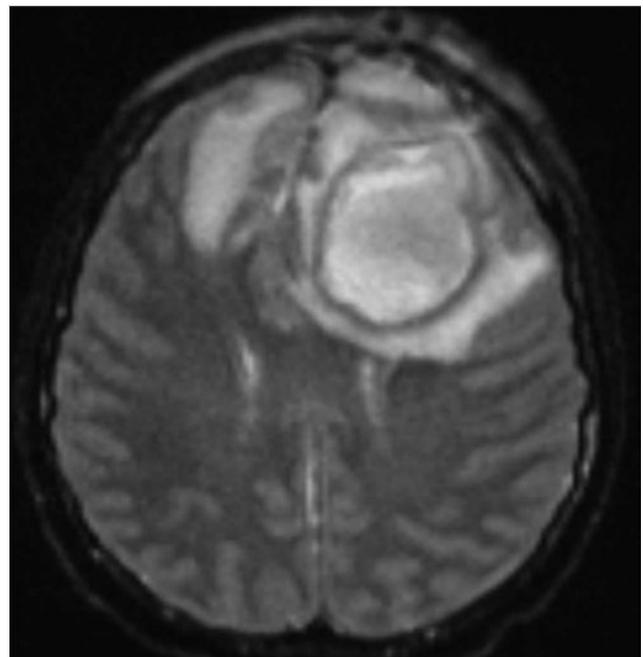


Fig. 79.4 Axial diffusion-weighted imaging sequence displaying the high-intensity inner contents of a left frontal brain abscess.

occur with toxoplasmosis abscesses and low-grade fibrillary astrocytomas.¹⁴

MR spectroscopy may also help narrow the differential diagnosis between cystic neoplasms, necrotic tumor, and purulent collections.² The existence of resonance peaks for succinate, acetate, lactate, and amino acids (such as valine and leucine) within the central cavity suggests the presence of a brain abscess.¹⁶ In contrast, cystic or necrotic tumors may exhibit a resonance peak only for lactate.¹⁷ MR spectroscopy combined with DWI and ADC mapping supplement conventional MR imaging findings in the diagnosis of pediatric brain abscesses.

Laboratory Studies

Multiple laboratory markers indicate the presence of infection in the setting of an intracranial abscess. These include peripheral leukocytosis and elevation of the C-reactive protein level and erythrocyte sedimentation rate. Lumbar punctures to acquire cerebrospinal fluid (CSF) are often contraindicated or



Fig. 79.5 Axial magnetic resonance imaging sequence with apparent diffusion coefficient mapping portraying low signal intensity of the central portion of the same left frontal brain abscess shown in ► Fig. 79.4.

provide a low yield in the setting of intraparenchymal abscesses.^{1,4,6} The CSF may show mild pleocytosis and an elevated protein level but typically exhibits a normal glucose concentration. Except with ventriculitis, the CSF Gram stain and cultures remain bland and sterile.⁶ Occasionally, culture data from blood or a contiguous site of infection suggest the culprit microorganism. However, blood cultures produce positive results in only a minority of cases.⁴

Additional Studies

In addition to defining an intraparenchymal abscess, the diagnostic work-up should search for predisposing factors. Concern for related sinus infections should prompt appropriate diagnostic imaging of the maxillary, ethmoid, frontal, and sphenoid sinuses (► Fig. 79.6). Because of the prevalence of cardiac anomalies and endocarditis in this population, echocardiography is an important tool in the diagnostic armamentarium. A thorough dental evaluation in children with brain abscesses may also reveal a surreptitious site of infection.⁶ In the absence of cardiac defects or obvious sites of contiguous infection, an evaluation for pulmonary infections or immunodeficiency may be valuable.

79.1.9 Treatment

Indications for Surgical Treatment

Like other intracranial lesions, brain abscesses warrant surgical consideration based on size, location, mass effect, and the patient's neurologic condition. In general, abscesses with a diameter larger than 2 to 3 cm deserve surgical attention because of mass effect.^{1,2,4,6} Furthermore, infratentorial abscesses merit

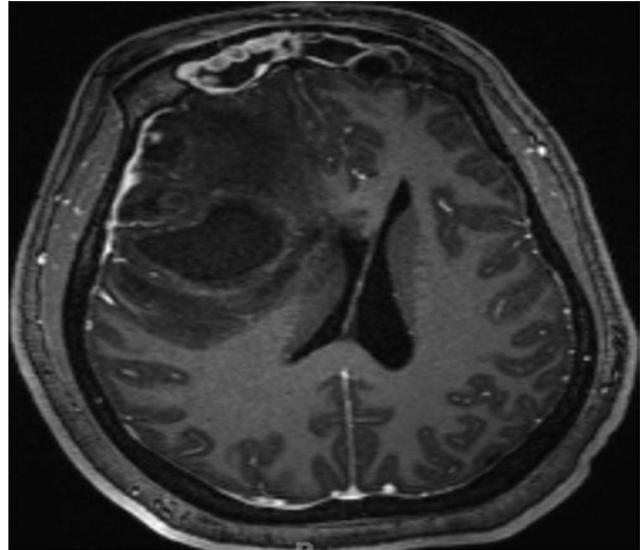


Fig. 79.6 Axial T1-weighted MR imaging sequence with gadolinium administration showing a right frontal intraparenchymal abscess with additional findings of bilateral frontal sinusitis and abnormal contrast enhancement.

surgical consideration because of the limited volume of the posterior fossa and risks for obstructive hydrocephalus or brainstem compression. Surgical intervention offers advantages of lowering the ICP and reducing mass effect, critical in children presenting with poor neurologic status. Additionally, surgical sampling usually provides a definitive diagnosis and identifies the offending microorganism.^{1,2,4} Surgical drainage also allows greater antibiotic efficacy; some antimicrobials lose their effectiveness when encumbered by many bacteria.^{2,4} Certain abscesses, including those in which *Nocardia*, helminths, parasites, or fungi are involved, respond poorly to medical therapy alone, requiring additional surgical intervention.⁴

Surgical Treatment

Surgical approaches for the treatment of brain abscesses include stereotactic needle aspiration and open excision. Both methods acquire samples for culture data and potentially alleviate mass effect. However, the two approaches differ greatly in regard to operative planning and invasiveness.

Stereotactic Needle Aspiration

Operative Technique

Stereotactic needle aspiration is a minimally invasive surgical approach to sampling and draining brain abscesses. The technique may be performed freehand or with intraoperative image guidance. Following appropriate placement of a standard bur hole or minimal craniotomy, the aspirating device can be advanced slowly into the necrotic core of the abscess. Intraoperative ultrasonography may help locate the abscess in real time during surgery. The biopsy needle trajectory should be chosen to avoid major vessels and eloquent cortex when possible. In rare cases of brainstem abscesses, transcerebellar or precoronal right paramedian transfrontal approaches have been used.^{1,13}

After the aspiration of purulent material, irrigation of the abscess cavity with antibiotic-impregnated fluid may enhance the treatment effect.¹ Stereotactic aspiration may be repeated in the context of multiple, residual, or recurrent abscesses.²

Advantages and Disadvantages of Stereotactic Aspiration

Stereotactic needle aspiration of brain abscesses offers several advantages over open craniotomy. As a minimally invasive approach, this technique involves less cortical exposure and damage to surrounding tissue.⁴ Aspiration allows the efficient decompression of purulent material in a relatively safe manner, with generally fewer complications than open approaches.^{1,2} Deep-seated lesions or those within eloquent cortex can be approached readily with needle biopsy, avoiding the greater risks of surgical excision. Brainstem abscesses, although accounting for fewer than 1% of intraparenchymal abscesses, similarly are favorable targets for minimally invasive techniques.¹³ Stereotactic aspiration also offers a safe approach to multiple brain abscesses in disparate regions. Finally, stereotactic aspiration can be used to approach abscesses in all stages of development, including early cerebritis, with a diagnostic yield near 95%.¹

Despite the numerous advantages of stereotactic aspiration, this minimally invasive technique may prove inadequate in certain settings. Aspiration may fail to decompress certain abscesses completely and may not prevent purulent reaccumulation. Suboptimal decompression may result from the high viscosity of purulent fluid or intra-abscess septa.¹³ Residual abscesses may require repeated stereotactic aspiration or the consideration of more aggressive surgical intervention.

Craniotomy and Abscess Resection

Operative Technique

Open craniotomy with lesion resection is an alternative approach to treating pediatric brain abscesses. Surgical excision also may be carried out with intraoperative image guidance. Wider calvarial opening and cortical exposure allow en bloc resection of the abscess wall and inner contents. During exposure and circumferential dissection, transcortical aspiration may be used urgently in the context of herniation. Once this and anesthetic maneuvers (hyperventilation, elevation of the head of the bed, administration of mannitol) lower the ICP, attention may be shifted to the abscess wall. However, friability of the parenchyma, proximity to eloquent cortex, and hemorrhage may preclude complete capsule resection. In addition to abscess removal, surgical excision allows the extrication of foreign bodies or skull fragments. Consequently, open craniotomy is the favored approach in brain abscesses secondary to penetrating head trauma.¹

Advantages of Open Craniotomy

Open craniotomy for abscess excision offers several benefits over stereotactic aspiration and nonsurgical management. The greater extent of pathologic tissue removal reduces concerns for residual mass effect postoperatively. Complete resection of the abscess capsule provides more tissue for histologic analysis, definitive therapy, and lower recurrence rates.^{1,3,8} Surgical excision generally offers the additional benefit of a shorter duration of antibiotic therapy postoperatively (3 to 4 weeks).⁴

Poor neurologic status of the patient also may necessitate more aggressive approaches up front. For instance, impending herniation may warrant open surgical intervention initially to lessen mass effect and maximize decompression.

Several types of pediatric brain abscesses, in addition to those associated with trauma, warrant strong consideration of open excision. Cerebellar abscesses may require open surgical intervention because of the confined space of the posterior fossa and concern for mass effect, obstructive hydrocephalus, or brainstem compression.^{1,2,4} In this context, suboccipital craniotomy allows wide posterior fossa decompression in addition to abscess resection.^{2,3} Multiple reports suggest lower rates of mortality and postoperative hydrocephalus with open resection than with stereotactic aspiration of cerebellar abscesses.^{1,3}

Recurrent intraparenchymal abscesses refractory to appropriate antimicrobial therapy and aspiration also are candidates for surgical resection.^{2,6} Certain abscesses, including fungal infections, show a poor response to stereotactic aspiration or medical therapy alone, ultimately requiring surgical excision.¹ Open craniotomy with abscess removal may be preferred for multiloculate abscesses because stereotactic aspiration may fail to drain each pocket of purulent fluid.⁴ Furthermore, an abscess in a location abutting the ventricular system may warrant surgical resection to prevent intraventricular spillage of the abscess contents. In the context of existing ventriculitis, open craniotomy should be performed urgently to débride infected tissue, irrigate the ventricles, and administer intraventricular antibiotics.² Additionally, brainstem abscesses may respond well to open exposure, debulking, and the drainage of purulent material with collapse of the capsule wall under direct visualization.¹³

Disadvantages of Open Craniotomy

Benefits of open craniotomy must be weighed against the disadvantages, including greater invasiveness, potentially longer operative times, greater surgical risk, and greater potential morbidity. Additional factors may disfavor open surgery. For instance, abscesses within stage I of formation (early cerebritis) may lack adequate development to warrant surgical excision. Multiple or deep-seated lesions and those within eloquent cortex may preclude aggressive resection, and serious medical comorbidities may elevate the surgical risk.¹

Endoscopically Assisted Abscess Evacuation

Neuroendoscopy represents an alternative or supplemental approach in many neurosurgical contexts. In the treatment of intraparenchymal abscesses, endoscopy recapitulates the minimally invasive nature of stereotactic aspiration while offering the direct visualization of abscess evacuation and antibiotic lavage (if desired).^{1,18} Direct inspection helps maximize the drainage of purulent fluid and allows the fenestration of septa in multiloculate abscesses.^{1,2,18} Despite sparse literature support showing benefit over other approaches, neuroendoscopy offers an alternative method of brain abscess evacuation deserving further attention.

Multidisciplinary Approaches

Regardless of the surgical approach used, brain abscesses should be managed with a multidisciplinary approach. Frontal

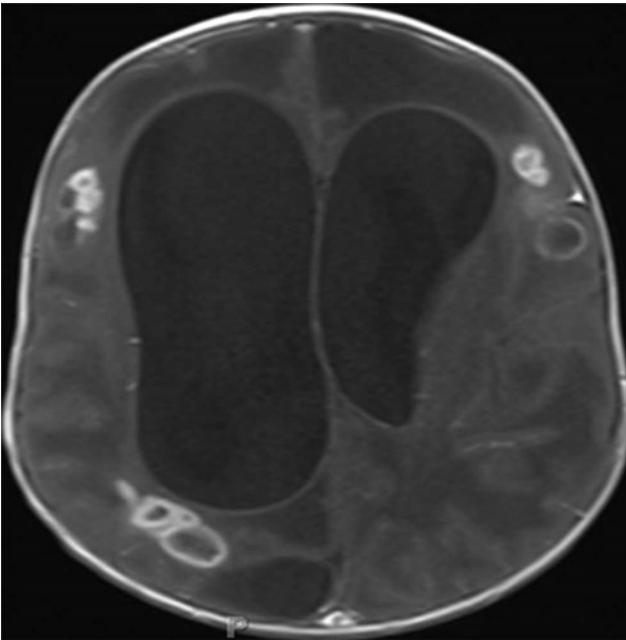


Fig. 79.7 Axial T1-weighted magnetic resonance imaging sequence with gadolinium administration depicting multiple brain abscesses in disparate locations.

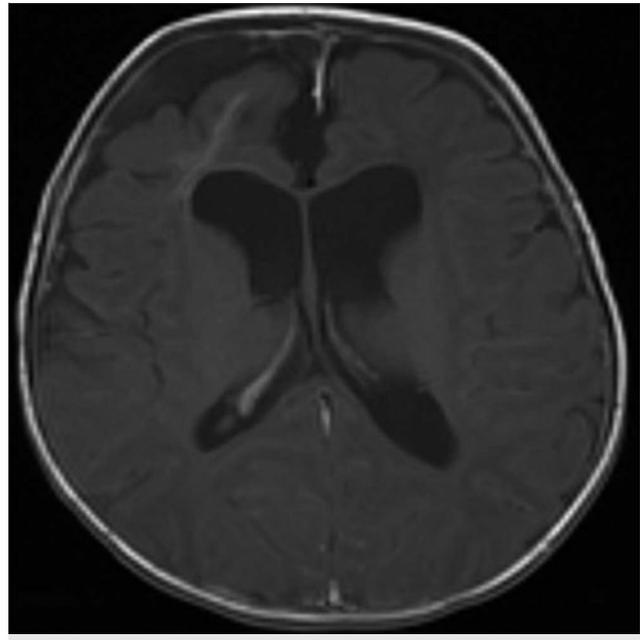


Fig. 79.8 Axial T1-weighted magnetic resonance imaging sequence with gadolinium administration showing evidence of residual contrast enhancement nearly 6 weeks following evacuation of a right frontal brain abscess.

lobe abscesses associated with facial infections or paranasal sinusitis can be managed by pediatric neurosurgeons and by colleagues from head and neck surgery or craniofacial plastic surgery. Similarly, temporal lobe or cerebellar abscesses extending from otitis media or mastoiditis should be approached through a collaborative effort between neurosurgery and otolaryngology.^{1,6} This combined approach may involve a craniotomy and mastoidectomy, either concurrently or at different times.^{3,19} Successful treatment of both the brain abscess and the source of infection decrease the risk for abscess recurrence.¹ Collaboration should extend beyond the surgical specialties to include infectious disease specialists and pediatricians for the safe and effective management of children with brain abscesses.

Antibiotic Therapy

Complementing surgical debulking, antibiotics are an integral component of the treatment of brain abscesses. Initial pharmaceutical selections are based upon the suspected microorganisms involved and the anticipated brain penetration of antimicrobials. Following empiric treatment, the antimicrobial regimen can be tailored based on culture data. The culture data may come from intracranial or extracranial sources, as long as no compelling reasons exist to assume differing identities of the microorganisms involved.

The therapeutic regimen typically entails at least a 4- to 6-week course of intravenous antibiotics, occasionally followed by oral antibiotics for 2 to 3 months.⁴ Some authors argue for a longer duration of intravenous antibiotics, up to 6 to 8 weeks, depending on the clinical scenario.^{2,13} The presence of multiple brain abscesses or immune system deficiency often warrants longer courses of intravenous antibiotics (► Fig. 79.7).¹ The unique setting of ventriculitis alters the treatment

regimen, requiring both systemic and intrathecal antibiotic administration.^{1,2}

Postoperative or Nonoperative Surveillance

Children treated surgically or nonsurgically for intraparenchymal abscesses require close clinical follow-up with neurologic examinations and serial imaging. Weekly or biweekly scans (CT or MR imaging) with contrast administration evaluate the regression or progression of disease.^{4,6} Abscesses that fail to decrease in size after 4 weeks of appropriate antibiotic therapy or that grow after 2 weeks of therapy urge for surgical reconsideration.¹ The bulk of intraparenchymal abscesses typically resolve on imaging by 12 to 16 weeks after the initiation of appropriate therapy. However, complete disappearance of contrast enhancement may require up to 6 months (► Fig. 79.8).¹ Following the discontinuation of antibiotics, serial imaging continues until complete radiographic resolution of all intraparenchymal abscesses.² Inadequate access to medical care limits postoperative surveillance in developing regions or Third World nations.

Treatment Alternatives

Empiric Antibiotic Therapy

Empiric antibiotic therapy is an important, potentially lifesaving component of the treatment of pediatric brain abscesses. However, broad-spectrum agents should not routinely supplant directed antibiotic therapy. Empiric therapy may precede purulent sampling to achieve clinical stability in a deteriorating patient. Preoperative antibiotic initiation often will not preclude microorganism isolation from intracranial sources.^{2,4}

Table 79.3 Examples of empiric antibiotic therapy in pediatric brain abscesses

Source of infection or predisposing condition	Suggested antibiotic regimen	Additional comments
Unknown source or etiology	Third-generation cephalosporin + vancomycin + metronidazole	Broad-spectrum regimen.
Sinusitis, otitis, mastoiditis, cyanotic congenital heart disease	Third-generation cephalosporin + metronidazole	Alternative regimen includes ampicillin/sulbactam, meropenem, or ciprofloxacin; use vancomycin for MRSA.
Penetrating head trauma, ventricular shunt infections, or endocarditis	Third-generation cephalosporin + vancomycin ± metronidazole	Covers MRSA and <i>Staphylococcus epidermidis</i> .
Bacterial meningitis	Third-generation cephalosporin + vancomycin	Covers cephalosporin-resistant <i>Streptococcus pneumoniae</i> .
Neonatal patient	Third-generation cephalosporin + ampicillin	Covers <i>Listeria monocytogenes</i> .
Dental infection	Penicillin + metronidazole	Alternative regimen includes ampicillin/sulbactam.
Immunodeficiency or immunosuppression	Third-generation cephalosporin + vancomycin + metronidazole	Use amphotericin for fungal infections and TMP/SMX for <i>Nocardia</i> infections.
Immunodeficiency (AIDS) and high level of suspicion for tubercular abscesses	Rifampicin + isoniazid + pyrazinamide + ethambutol	

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; TMP/SMX, trimethoprim/sulfamethoxazole.

Alternatively, antibiotics can be withheld until the acquisition of brain abscess specimens, given patient stability. This practice prevents any potential sterilization of intraoperative cultures.^{1,2}

Broad-spectrum antibiotics should be selected to maximize coverage based on the suspected source of infection (► Table 79.3). Typical regimens include a third-generation cephalosporin with appropriate brain penetration, such as cefotaxime, ceftazidime, or ceftriaxone. The increasing prevalence of methicillin resistance in *S. aureus* and *S. epidermidis* favors vancomycin use in abscesses associated with penetrating head trauma, endocarditis, or ventricular shunts.⁴ Metronidazole joins the antibiotic regimen for abscesses associated with sinus or ear infections or cyanotic congenital heart disease.^{2,4} Neonatal brain abscesses concerning for *Listeria monocytogenes* require the addition of ampicillin.⁴

Antibiotic Therapy with Culture Sampling of Other Infected Sites

Diminutive intraparenchymal abscesses (<2 to 3 cm) with an identified source and suspected microorganism can be treated nonsurgically with appropriate antibiotics.^{1,2,4,6}

Patients who lack neurologic deficits or signs of elevated ICP and who are poor surgical candidates may benefit from medical treatment alone.^{1,2} Alternative culture sources include blood, sputum, and purulent drainage from the ears, sinuses, or contiguous sites of infection.² Disadvantages of the nonsurgical approach include a higher rate of recurrence.¹ The growth of brain abscesses or the appearance of new neurologic deficits despite antimicrobial therapy warrants reconsideration of surgical intervention.

Steroid Therapy

The role of corticosteroids in the treatment of pediatric brain abscesses remains controversial. Although they reduce vasogenic

edema and lowering ICP, steroids adversely affect the treatment of infections.^{2,3} Corticosteroids act as immunosuppressants and decrease antimicrobial penetration into the brain.⁴ These factors limit the use of steroids to clinically unstable children with brain abscesses causing edema and ICP elevation.¹ If initiated, steroids should be continued for a short duration to minimize their disadvantages.

Antiepileptic Agents

Because of mass effect and cortical irritation, brain abscesses carry a risk for propagating seizure activity. Seizures may occur in delayed fashion, with a latency period of up to 3 years.¹ Older reports suggest that only 50% of seizures developing in pediatric patients with intraparenchymal abscesses occur within the first year after diagnosis.¹ In the context of witnessed or documented seizures, anticonvulsants are an integral component of the therapeutic regimen for brain abscesses. However, clinical trial evidence is not available to support the use of prophylactic antiepileptics in children with intraparenchymal abscesses.⁶

Because of the seizure risk associated with brain abscesses and surgical excision, antiepileptic medications are usually recommended prophylactically.¹ Anticonvulsant therapy typically continues for a short duration except in the presence of known seizure activity.⁶ Alternatively, some authors recommend a prolonged duration of prophylactic anticonvulsant therapy.² Drawbacks of antiepileptics include medication side effects and pharmacologic interactions with antibiotics.⁶

79.1.10 Prognostic Factors

The clinical and neurologic status upon presentation significantly affect the prognosis for children with brain abscesses. Mental status or behavioral changes and lethargy correlate with worse outcomes, whereas early detection and intervention

before patient decompensation increase the chances for healthy survival.^{1,2} A delayed presentation is a poor prognostic indicator, especially in developing regions with limited access to care.⁶ The rapid progression of neurologic deficits and a moribund or comatose appearance similarly predict higher rates of morbidity and mortality.

Specific patient or abscess characteristics influence prognosis as well. Younger infants, especially those younger than 1 year, tend to fare worse than older children with brain abscesses.⁴ The coexistence of seizures, hydrocephalus, or meningitis with brain abscesses further worsens the prognosis.¹ Immunocompromised patients typically experience more complicated clinical courses than do their immunocompetent counterparts.⁶ The presence of multiple abscesses or of highly virulent pathogens also portends a worse prognosis.^{1,4} Lesions residing near the ventricles or subarachnoid cisterns are associated with increased risks for poor outcomes. The leakage of abscess contents into the ventricular system or subarachnoid space leads to ventriculitis or fulminant meningitis. The patients exhibit rapid clinical deterioration and may progress to death.^{1,5,6}

79.1.11 Outcomes

Several factors have improved the diagnosis and treatment of brain abscesses over the past 80 years. These include enhanced imaging modalities, stronger antibiotics, advanced surgical techniques, and better culturing methods.^{1,6} The mortality rates for brain abscesses before the discovery of antibiotics ranged between 40 and 60%.¹ Current mortality rates for pediatric brain abscesses overall have declined to 4 to 15%, and those for infratentorial abscesses to 11 to 41%.^{1,3,4}

Although displaying similar trends, the morbidity rates for pediatric brain abscesses remain high, reaching 33% in clinical series.⁴ Common examination findings after treatment include hemiparesis or weakness within one extremity, visual field cuts, and cognitive deficits.^{1,6} Younger children exhibit susceptibility to impaired intellectual development in the setting of brain abscesses.¹ Infratentorial abscesses may lead to delayed hydrocephalus requiring shunt placement, even after successful excision.³ Additionally, supratentorial abscesses may cause delayed or persistent seizure activity.¹

79.1.12 Complications

Several complications are associated with surgical approaches to abscess treatment. Hemorrhage is an important risk with both stereotactic aspiration and open craniotomy. The occurrence of hemorrhage in either operative technique correlates with a worse overall prognosis.⁶ Additional risks for CSF leakage, seizures, and infarction represent important considerations regarding open craniotomy.⁶ With either surgical approach, the entry of abscess contents into the ventricular system or subarachnoid space is a devastating and potentially fatal complication.^{1,6}

79.1.13 Third World Perspectives

The principles of the management of pediatric brain abscesses in Third World countries are similar to the principles followed in developed nations, but with important caveats. Regarding

etiology, chronic otitis media is a predominant cause of intraparenchymal abscesses, along with cyanotic congenital heart disease (e.g., tetralogy of Fallot).^{2,12,20} Chronic suppurative otitis media accounts for up to 30% of patients treated yearly at major tertiary care centers located in developing regions, such as southern India.¹⁹ A retrospective review in Thailand related the high preponderance of pediatric brain abscesses and otogenic infections to low socioeconomic status and inadequate access to medical care.² Resulting delayed or insufficient treatment of otic and other infections subsequently predisposes to brain abscess formation.^{2,12,19} Given these factors, brain abscesses are a frequent neurosurgical pathology in developing nations. For instance, the Korle Bu Teaching Hospital in Ghana reported a 4.8% incidence of brain abscesses (70% occurring in patients younger than 20 years) among neurosurgical admissions over a recent 4-year period.⁷

Most pediatric brain abscesses in developing countries result from the contiguous spread of infection.⁷ Although culture techniques limit microbiological data, the causative pathogens most commonly isolated mirror those in the United States—*Streptococcus* and *Staphylococcus*.⁷ Culture data regarding anaerobes often cannot be obtained, given suboptimal laboratory techniques.⁷ *Bacteroides fragilis* is a predominant anaerobe isolated when culturing techniques are available, similar to findings in developed nations.¹² The rising prevalence of AIDS in developing nations and the limited availability of appropriate treatment regimens increase the risks for opportunistic infections. Regions of endemicity show an increasing frequency of brain abscesses involving *Toxoplasma gondii*, *Nocardia*, *Aspergillus*, and *Candida*.⁷

The diagnosis and treatment paradigms in third world countries match the availability of resources. Because of the expense and paucity of MR imaging scanners, CT with contrast administration is the primary imaging modality implemented. In certain settings, individual patient responsibility for covering the costs of MR imaging further limits its use. Limited access to CT scanners and hospitals with neurosurgical services may delay diagnosis, resulting in worse neurologic status upon presentation.²⁰ When discovered, pediatric brain abscesses in developing nations are often managed with bur hole craniotomy and aspiration, frequently under local anesthesia.⁷ Typically, the lack of sufficient equipment and resources fosters freehand approaches.

Decisions regarding treatment regimens, including parenteral antibiotics, anticonvulsants, and corticosteroids, reflect the trends in developed nations but also respect the limited availability of resources in developing nations. Antibiotic therapy typically lasts for 4 to 6 weeks, with modifications based on the antimicrobials available and the virulence of the pathogens.^{7,19} Given the advent of CT and improved antimicrobial agents, the mortality and morbidity associated with pediatric brain abscesses have significantly declined in developing regions. However, complicating factors like delayed presentation, limited access to care, and unavailability of optimal treatment regimens force these rates to remain high. A retrospective study at Korle Bu Teaching Hospital in Ghana reported a 10.9% mortality rate for brain abscesses in series of patients that included mostly children.⁷ A prospective study in Mumbai, India, from 2001 to 2005 showed a mortality rate of 13.3% for brain abscesses in patients younger than 20 years.¹²

79.2 Encephalitis

79.2.1 Overview

Encephalitis is an inflammatory condition of the brain reflecting infectious or noninfectious etiologies. It causes global or focal neurologic impairment. The term *meningoencephalitis* refers to inclusion of the meninges in the inflammatory process. Many viruses (herpes simplex virus, mumps virus) cause systemic symptoms with rare or benign central nervous system (CNS) involvement, whereas a few viruses (rabies virus, Japanese encephalitis virus) affect the CNS primarily.²¹ Viral encephalitides account for most instances of acute encephalitis, with 1,000 to 2,000 cases yearly (► Table 79.4).^{22,23} Despite advanced diagnostic techniques, the etiology of encephalitis remains

unknown in up to 60% of cases, as shown in the California Encephalitis Project.²²

79.2.2 Clinical Presentation

CNS inflammation occurs via primary infection or secondarily after infection or vaccination. Pathophysiologic mechanisms of acute viral CNS infection include hematogenous dissemination and intraneuronal transmission.^{21,23} Affected patients may experience the classic triad of fever, headache, and altered mental status.^{21,22} Additional global or focal neurologic deficits often correlate with specific viral pathogens (► Table 79.5). Neurologic findings may include changes in speech, executive function, behavior, or level of consciousness; deficits in cranial nerves or strength; and seizures.^{21,22}

Table 79.4 Examples of acute viral encephalitis occurring in the pediatric population

Viral families causing encephalitis	Current or proposed treatment or prevention
Bunyavirus encephalitis La Crosse encephalitis virus California serogroup viruses Toscana virus	Ribavirin (intravenous)
Flavivirus encephalitis Dengue virus Japanese encephalitis virus Powassan encephalitis virus St. Louis encephalitis virus Tick-borne encephalitis viruses West Nile virus	Vaccine available Interferon- α -2b Vaccine available (Europe) Interferon- α , intravenous immunoglobulin
Herpesvirus encephalitis Cytomegalovirus Epstein-Barr virus Herpes simplex viruses 1 and 2 Human herpesvirus 6 Varicella-zoster virus	Ganciclovir, foscarnet, or cidofovir Acyclovir Ganciclovir, foscarnet, or cidofovir; vaccine available Acyclovir, steroids; vaccine available
Orthomyxovirus encephalitis Influenza A virus, influenza B virus	Vaccine available
Papovavirus encephalitis JC virus	
Paramyxovirus encephalitis Rubeola virus (measles virus) Mumps virus Nipah virus	Vaccine available Vaccine available Ribavirin (intravenous)
Picornavirus encephalitis Enterovirus 71 Other enteroviruses Poliovirus	Vaccine available
Reovirus encephalitis Colorado tick fever virus	Ribavirin (experimental)
Retrovirus encephalitis Human immunodeficiency virus	Antiretroviral therapy
Rhabdovirus encephalitis Chandipura virus Rabies virus	Ribavirin (intravenous), iatrogenic coma; vaccine available
Togavirus encephalitis Eastern equine encephalitis virus Venezuelan equine encephalitis virus Western equine encephalitis virus	

Table 79.5 Common clinical findings associated with viral encephalitides

Viral etiology	Unique clinical findings	Patient characteristics or mechanism of exposure
Chandipura virus	Seizures, focal neurologic deficits	Children in southern India
Cytomegalovirus	Hearing loss, seizures, mental retardation, developmental delay	Congenital infection, immunocompromised
Eastern equine encephalitis virus	Seizures, fulminant course to coma; high mortality rate	More common in older adults than in children
Enterovirus	Flaccid paralysis	
Herpes simplex virus	Seizures, focal neurologic deficit; temporal lobe location	HSV-2 in neonates, HSV-1 in infants and children
Japanese encephalitis virus	Seizures, tremor, rigidity, masklike facies; flaccid paralysis (uncommon)	Mosquito bite transmission
JC virus	Progressive multifocal leukoencephalopathy (PML)	Immunocompromised
La Crosse virus	Focal seizures, weakness, paralysis, delirium, coma	More common in children than in adults, mosquito bite transmission
Rubeola virus (measles virus)	Subacute sclerosing panencephalitis (SSPE), cognitive decline, incoordination	Immunocompromised
Nipah virus	Brainstem involvement, autonomic instability, hypotonia; small-vessel vasculitis within cerebral white matter	Pig farm workers, fruit bat exposure; mostly in Bangladesh and India
Poliovirus	Flaccid paralysis	Lack of vaccination, immunocompromised
Powassan virus	Memory deficits, confusion, seizures; hippocampal predilection	Tick bite exposure; northeastern United States and Canada
Rabies virus	Lability, behavioral changes, autonomic abnormalities	Animal bite or bat exposure
Tick-borne virus	Flaccid paralysis, transverse myelitis	Tick bite exposure
Varicella-zoster virus	Cerebellitis, temporal lobe deficits	Immunocompromised
West Nile virus	Flaccid paralysis, tremors	Mosquito bite transmission; serious sequelae more often in elderly or immunocompromised
Western equine encephalitis virus	Seizures	Mostly infants affected

79.2.3 Diagnosis

MR imaging, CSF analysis, and clinical history are the primary diagnostic tools in acute encephalitis. The clinical history focuses on age, symptoms, exposures, travel, vaccination history, immune status, geography, and seasonal timing.²³ Key distinguishing features that favor encephalitis over meningitis include altered sensorium progressing to behavioral or cognitive changes, coma, seizures, or focal deficits.²³ The examination incorporates a neurologic assessment and general evaluation for skin rashes and sites of exposure.

Imaging findings vary among the acute viral encephalitides. Nonspecific MR imaging findings include T2 hyperintense lesions with variable mass effect and edema.²³ Classic MR imaging findings include temporal or sylvian fissure hemorrhagic inflammation in herpes simplex virus (HSV) encephalitis and diffuse white matter lesions in progressive multifocal leukoencephalopathy (PML; associated with JC virus).²³ With gadolinium contrast enhancement, the lesions may appear diffuse and involve the meninges.²³ Other para-infectious encephalitides exhibit recognizable MR imaging characteristics, including asymmetric white matter lesions in acute disseminated encephalomyelitis (ADEM) and symmetric T2 hyperintense periventricular white matter lesions in acute necrotizing encephalopathy

(ANE).²² Electroencephalography (EEG) is another diagnostic modality potentially useful in acute encephalitis. Although diffuse abnormalities appear in various encephalitides, focal aberrant activity may be seen in HSV encephalitis and subacute sclerosing panencephalitis (SSPE) caused by measles virus.^{22,24}

CSF analysis includes Gram stain, cell counts, molecular profiles, culture, and polymerase chain reaction (PCR). Although the cell count, glucose level, or protein level may appear unremarkable, many viral encephalitides cause mild elevations of CSF monocytes or protein.²¹ Depressed CSF glucose levels may indicate bacterial or HSV infection.²² Routine CSF viral PCR studies search for HSV, enterovirus, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) infection. With appropriate clinical suspicion, additional CSF studies include immunoglobulin M (IgM) analysis for Japanese encephalitis virus, VZV, West Nile virus (WNV), or *Borrelia* antibodies.²²

79.2.4 Treatment

Empiric therapy is directed at potential causes of both bacterial meningitis and acute viral encephalitis. Among the few effective antiviral agents, acyclovir is the primary empiric agent used in children.^{21,22} A typical broad-spectrum regimen includes acyclovir, vancomycin, and a third-generation cephalosporin (plus

ampicillin in neonates).²² Antibiotics should be tailored and modified upon return of the CSF and other diagnostic studies. Following empiric therapy, supportive care and close monitoring are the primary management strategies for viral encephalitis lacking definitive treatment options. Measures to control elevated ICP can reduce the primary mortality factor in fulminant viral encephalitis.²⁵

79.2.5 Prevention

For several viral encephalitis, exposure control and vaccination are the primary methods to combat infection. Vaccines are readily available for Japanese encephalitis, polio, rabies, influenza A and B, mumps, and measles viruses.^{21,22} Before major immunization efforts were undertaken for children in the United States, measles virus and mumps virus were the two primary causes of acute encephalitis and post-infectious encephalitis (SSPE).²² However, vaccines have nearly eradicated or significantly reduced the prevalence of these and other viral encephalitis. Vector control and the avoidance of animal exposure are helpful adjuncts for the prevention of many viral encephalitis.^{21,26}

79.2.6 Selected Acute Viral Encephalitis

Herpes Simplex Virus Encephalitis

Although it is a frequent cause of systemic illness, HSV infiltrates the CNS uncommonly beyond infancy.²¹ However, because of the widespread nature of HSV infection, this virus accounts for most cases of non-epidemic acute encephalitis in the United States, with an incidence between 1 in 250,000 and 1 in 500,000.^{21,27} Approximately one-third of cases of HSV encephalitis occur in pediatric patients.²⁴ Furthermore, the frequency of CNS involvement in infantile HSV infection reaches nearly 50%.²⁷ HSV encephalitis exhibits Cowdry type A intranuclear inclusions histologically and shows positive results on PCR analysis of the CSF.^{21,24}

The specific variant of HSV encephalitis differs between neonates and older children. Neonatal patients acquire HSV-2 infection primarily during passage through an infected maternal birth canal.²⁷ Infection spreads hematogenously and may result in diffuse areas of hemorrhagic necrosis and encephalomalacia.^{24,27} In contrast, infants and older children with HSV-1 encephalitis show unilateral temporal involvement that ultimately spreads to involve both temporal lobes.²¹ The mechanism of disease spread in HSV-1 infection involves retrograde transport along axons.^{23,24} Because of its predilection for the temporal lobe, HSV encephalitis may result in clinical findings of aphasia, seizures, or other focal deficits.^{21,24} Neonates with encephalitis due to HSV-2 infection have a worse outcome than those with HSV-1 infection.²¹

In contrast to many other encephalitis, HSV encephalitis responds favorably to direct therapy with acyclovir. Despite this effective treatment, pediatric mortality and morbidity remain high. The age-independent mortality of patients with treated HSV encephalitis reaches 28%, and children have a worse prognosis.²¹ Newer treatment regimens involving longer durations

of therapy (21 days) and higher doses of acyclovir (60 mg/kg per day as opposed to the standard 30 mg/kg per day) have improved outcomes in neonatal HSV encephalitis.^{23,24}

Enterovirus Encephalitis

Enteroviral encephalitis typically exhibits a low level of morbidity, with cognitive changes, lethargy, and seizures.²³ In contrast, a Taiwanese 1998 epidemic associated with enterovirus 71 had higher rates of pediatric morbidity and mortality (19% in children younger than 5 years).²¹ Exhibiting preferential brainstem involvement, enterovirus 71 may induce tremors, ataxia, cranial nerve deficits, or neurogenic shock. Excluding the polio vaccine, no definitive antimicrobial regimens or vaccines exist to combat enteroviral encephalitis.²¹

West Nile Virus Encephalitis

Emerging in the 1990s and reaching North America by 1999, a more virulent subtype of WNV has caused several outbreaks owing to its broad host (birds) and expansive vector (*Culex* mosquitoes).^{21,22,28} However, only 1 to 2% of WNV infections result in acute encephalitis.^{22,26,28} Furthermore, children account for a minority of infected patients (<10%) and develop neurologic sequelae less frequently than adults.^{22,26,28} Neurologic deficits in WNV encephalitis include acute flaccid paralysis, disorientation, stupor, dyskinesias, and tremors.^{21,22,26,28} Proposed treatment regimens include interferon- α and intravenous immunoglobulin, but no direct antiviral therapies or vaccines exist.^{21,26}

La Crosse Encephalitis

La Crosse encephalitis virus affects primarily school-age children and is the most common endemic cause of acute viral encephalitis in America since the 1960s, accounting for 30 to 180 cases yearly.²⁵ Pediatric patients may present with focal seizures, weakness, or paralysis and progress from delirium or lethargy to coma.^{21,25} Mortality rates for La Crosse encephalitis fall below those of other viral encephalitis, while morbidity rates reach 10 to 15%.²¹ Clinical series and case reports describe the use of intravenous ribavirin as therapy for La Crosse virus encephalitis.^{22,25}

Japanese Encephalitis

Transmitted through *Culex* mosquitoes, Japanese encephalitis virus mainly affects children in regions of China, southeastern Asia, India, Pakistan, eastern Russia, the Philippines, and Australia where it is endemic.^{21,29} Although fewer than 1% of infections result in encephalitis, pediatric patients may develop altered mental status, seizures, tremors, rigidity, and acute flaccid paralysis.^{21,29} MR imaging findings include mixed-intensity lesions within the diencephalon and mesencephalon, and CSF analysis may detect IgM antibodies.²¹ The prognosis for children with Japanese encephalitis remains poor, with mortality and neurologic morbidity rates reaching 30% and 50%, respectively.²⁹ Management involves pre-exposure vaccination and post-exposure supportive care.²¹

Rabies Encephalitis

Exhibiting high neurotropism, the rabies virus spreads intraneuronally to preferentially infect neurons of the limbic system and cause isolated CNS infection.^{21,22} Primary modes of human inoculation include exposure to bats and animal bites, especially bites from infected dogs in developing nations.²¹ Following an incubation period typically ranging from 20 to 60 days, neurologic symptoms may progress from lability, behavioral changes, and weakness to coma or death.^{21,22}

Salivary reverse-transcriptase PCR aids the diagnosis, and histology portrays intracytoplasmic Negri bodies.²¹ Without intervention, the mortality of rabies encephalitis reaches 100%. Management involves prevention, pre-exposure vaccination, and post-exposure vaccination with the rabies immunoglobulin and vaccine.²¹

Tick-Borne Encephalitides

Tick-borne encephalopathy results from viral or bacterial etiologies and includes tick-borne encephalitis, Lyme neuroborreliosis, and Rocky Mountain spotted fever. Caused by a member of the flavivirus family, tick-borne encephalitis exhibits a milder course in children than in adults, with occasional residual cognitive impairment and a low mortality rate.³⁰ Although no direct treatment of tick-borne encephalitis exists, management involves active immunization with vaccines (in Europe) and prevention through the avoidance of tick bites or early tick removal.³⁰ Post-exposure prophylaxis with immunoglobulin G (IgG) is contraindicated in children younger than 15 years because of the potential induction of a severe (even fatal) clinical course.³⁰

Members of the bacterial spirochete family, *Borrelia* species cause Lyme borreliosis. An erythema migrans rash develops at the tick exposure site, and the hematogenous spread of spirochetes may induce neuroborreliosis 4 to 8 weeks later, signified by meningoencephalitis, radiculitis, or facial nerve palsy in children.³⁰ Treatment for neuroborreliosis includes doxycycline (contraindicated in children younger than 8 years), amoxicillin, ceftriaxone, or penicillin G.³⁰ As a less common cause of bacterial encephalitis, Rocky Mountain spotted fever may induce behavioral changes, delirium, seizures, or coma following the presentation of a macular hemorrhagic rash.³⁰ The sequelae of Rocky Mountain spotted fever in children can be treated with doxycycline or levofloxacin.³⁰

Acute Disseminated Encephalomyelitis

With characteristics similar to those of multiple sclerosis and neuromyelitis optica, ADEM is a demyelinating disease that follows an infection, vaccination, or nonspecific illness. Although it is the most common white matter disease in children, ADEM occurs infrequently, with an incidence of 0.4 per 100,000.²³ A large series of pediatric ADEM cases in 2003 reported a median age at onset of nearly 7 years, with more than 50% of children having had a preceding illness or vaccination.²² This autoimmune inflammatory condition affects the CNS white matter bilaterally and often asymmetrically.^{22,23} With nonspecific CSF findings of lymphocytic pleocytosis and elevated protein, the diagnosis of ADEM relies upon MR imaging and clinical history.²³ Neurologic symptoms include motor deficits, ataxia,

seizures, visual or speech abnormalities, impaired cognition, behavioral changes, and autonomic dysregulation.^{22,23} The diagnosis must be differentiated from multiple sclerosis, which requires a multiphasic presentation. First-line therapy for ADEM involves intravenous steroids (corticosteroids for 3 to 5 days or dexamethasone for 10 days), followed by an oral prednisone taper over 14 to 21 days (or longer).^{22,23} Children with a poor response to steroids may undergo immunoglobulin therapy or plasma exchange.²²

Pearls

- Pediatric brain abscesses require early diagnosis and intervention to minimize patient morbidity and mortality. Children presenting with fever, headaches, altered mental status, and coexisting sites of infection should elevate clinical suspicion.
- Frequently contraindicated because of mass effect, CSF acquisition via lumbar puncture is often of little diagnostic utility in brain abscesses lacking ventricular or subarachnoid extension.
- Broad-spectrum antibiotics should be initiated early in an unstable patient. However, empiric agents should never replace culture-directed therapy.
- Stereotactic aspiration offers a minimally invasive approach to acquiring culture data and reducing mass effect. The rate of abscess recurrence is typically higher with this approach than with open excision.
- Open craniotomy for abscess resection allows greater decompression and reduction of mass effect, but with greater surgical risk and morbidity.
- Acute deterioration in a pediatric patient with a brain abscess may signal intraventricular rupture or subarachnoid dissemination of the abscess contents. Ensuing ventriculitis or fulminant meningitis may be fatal and requires urgent intervention.
- Acute viral encephalitis often presents with fever, altered mental status, focal neurologic deficit, and/or seizures.
- Few antiviral agents besides acyclovir are available to combat acute encephalitis. Many treatment regimens rely on post-exposure vaccination or supportive care.
- Pre-exposure vaccination, vector control, and other preventive measures are successful strategies to reduce the occurrence of acute infectious encephalitis.

79.3 Acknowledgements

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80 Tuberculosis, Parasitic Infestations, and Fungal Infections

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Although tuberculosis, fungal infections, and parasitic infestations of the nervous system have declined in importance in developed countries over the course of the 20th century, they have received renewed attention in recent years because of their impact on vulnerable groups, such as persons infected with the human immunodeficiency virus (HIV) or receiving immunosuppressive treatment. The increased migration of people in the era of globalization has also played a significant role because these infections remain important causes of neurologic disease in developing countries. Patients may present either with focal lesions that require surgical management or with widespread central nervous system (CNS) disease, such as meningitis, which in this setting is often complicated by hydrocephalus.

80.1 Tuberculosis

The tide appears to be turning against tuberculosis (TB) once again; although there were 8 million new cases worldwide in 2010, with 1.1 million deaths in HIV-negative patients and 350,000 deaths from HIV-associated TB, there has been a fall in the absolute number of cases since 2006, sustaining hope that the Millennium Development Goal of falling TB incidence rates will be achieved by 2015.¹ The number of new cases in 2011 fell among both U.S.-born and foreign-born persons in the United States.²

TB is caused by infection with an aerobic, nonmotile, rod-shaped bacterium readily identified on Ziehl-Neelsen (acid-fast bacillus) stain, almost invariably *Mycobacterium tuberculosis*. There is an important distinction between asymptomatic infection, which is common, and disease, which occurs in a minority of cases.

Pulmonary infection results from the inhalation of aerosolized droplets; phagocytes carry bacilli from the alveoli to regional lymph nodes, which enlarge and form the so-called primary complex with the lung lesion. Lymphatic and hematogenous dissemination to other organs also occurs in the first few weeks, which in its most severe form presents as miliary TB. Macrophages are the primary cells infected by *M. tuberculosis*, and mycobacterial antigens trigger T helper cells to produce interferon- γ , which activates the macrophages to become bactericidal. Activated macrophages secrete tumor necrosis factor (TNF) and produce the epithelioid cells and giant cells typical of tuberculous granulomas.³

In approximately 95% of cases, infection is controlled by this activation of cell-mediated immunity in the host, but in some patients, the lung lesion gives rise to progressive pulmonary disease or extrapulmonary spread, resulting in systemic miliary TB or isolated TB in any of the organs seeded.³ Secondary TB may follow many years later as a consequence of reduced host immunity, with reactivation of a latent focus or exogenous reinfection. CNS involvement occurs in approximately 1% of persons with TB⁴ and takes the form of tuberculous meningitis (TBM),

focal parenchymal lesions, such as tuberculomas or tuberculous abscesses, or tuberculous osteomyelitis, either of the skull or vertebrae (Pott disease, discussed in Chapter 81).

80.1.1 Tuberculous Meningitis

TBM is the most lethal form of systemic tuberculosis, and in some parts of the world it is the most common form of bacterial meningitis; in sub-Saharan Africa, this has largely happened on the back of the HIV pandemic.^{5,6} In general, TBM is typically a disease of young children in countries with a high incidence of the disease, whereas in countries with a low incidence, it is seen more often in adults, arising from reactivation of a dormant focus.⁵

Rich and McCordock proposed that mycobacteria spread via the blood to the CNS, where a parenchymal or subpial focus develops and the cerebrospinal fluid (CSF) space is entered when the so-called Rich focus ruptures into the subarachnoid space.⁷ Other possible routes into the CSF include rupture of a focus in the choroid plexus or elsewhere in the ventricle, spread from a contiguous bony structure, and delayed rupture of a previously controlled caseous focus. The characteristic feature is a thick, gelatinous exudate in the basal cisterns, common consequences of which are hydrocephalus and cerebrovascular involvement; both of these contribute to ischemia, raised intracranial pressure (ICP), and parenchymal injury.^{8,9}

More than half of all cases may have infarcts on magnetic resonance (MR) imaging or at autopsy, and although vasospasm and external compression of the basal arteries of the circle of Willis and their perforators may play a role, histologic studies show infiltrative, proliferative, and necrotizing changes as well as thrombosis in arteries and veins.¹⁰ Infarcts are found in the diencephalon or the cortex¹¹⁻¹³ and may develop even after treatment has been started and the ICP is normalized.¹⁴ Stroke in TBM occurs in up to 56% of cases, with an even higher prevalence in childhood.^{15,16} Vascular complications in TBM are therefore common and often fatal, making ischemia the most important reason that patients with tuberculous hydrocephalus (TBH) fail to improve clinically or even deteriorate further despite aggressive medical treatment and the early treatment of hydrocephalus.¹⁷

Hydrocephalus is present in 70% of TBM cases¹⁸ and is due mainly to blockage of the basal cisterns by tuberculous exudate in the acute stage and adhesive leptomeningitis in the chronic stage. Although typically communicating hydrocephalus develops, noncommunicating hydrocephalus is reported to occur in approximately 17% of cases as a result of obstruction at the outlet foramina of the fourth ventricle or the aqueduct by meningeal exudate, edema, or a tuberculoma,¹² or a combination of these factors.

The diagnosis of TBM is made in the appropriate clinical context on the basis of CSF analysis results supported by appropriate imaging findings. This is more easily said than done, and clinical research in this area has been hampered by the lack of

standardized diagnostic criteria.¹⁹ Perhaps the greatest challenge is to make the diagnosis early, which is difficult because of the nonspecific early features of TBM; a review of 554 pediatric cases seen over a 20-year period found that 91% of patients had poor weight gain or weight loss, and this may be an important early clue.¹⁸ The prevalence of the disease in the community determines the degree of clinical suspicion. The diagnosis is suggested by a history of a TB contact and a positive tuberculin skin test or Mantoux test result; the chest X-ray may show findings typical of pulmonary TB, and the organism may be identified or cultured from sputum or gastric washings. New molecular diagnostic tools, such as the fully automated amplification system Xpert MTB/RIF, have been introduced into clinical practice and are being validated for CNS disease, but major challenges in scale-up exist in countries where the need is greatest.²⁰

The gold standard for the initial diagnosis of TBM is the demonstration of acid-fast bacilli under the microscope, but the yield is low unless large volumes of CSF are collected. Microscopy typically shows pleocytosis, with a cell count seldom greater than 500/mm³. Lymphocytes predominate, although polymorphonuclear leukocytes may on occasion be more numerous, particularly in the early phase of the disease. Typically, the CSF glucose is low and the protein is elevated. *M. tuberculosis* is particularly slow-growing, so culture plays no role in the initial diagnosis and management of the disease, but it becomes important should one not see an adequate clinical response, because multidrug resistance or extended drug resistance should be considered.

The typical appearance of TBM on computed tomography (CT) is often described as a triad of contrast enhancement of the basal meninges with hydrocephalus and infarcts²¹ (► Fig. 80.1). Hyperdensity may be noted in the basal cisterns before the administration of contrast, and this represents the cisternal exudate.²² Low densities related to cerebral ischemia are common, particularly in the vascular territory of the middle cerebral artery, involving the lenticulostriate and thalamoperforating vessels in the so-called TB zone adjacent to the basal ganglia.^{15,17} Occasionally, accompanying tuberculomas or tuberculous abscesses may be noted. It has been shown that there is no direct correlation between ventricular size and ICP in TBM.²³

Antituberculous medication comprises an initial intensive phase with four drugs; isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) are recommended together with either streptomycin, ethambutol, or ethionamide. Some authors advocate treatment with four drugs for 6 months,¹⁸ whereas others prefer 9 to 12 months.^{24–26} Pyridoxine should be prescribed with INH to prevent peripheral neuropathy. The emergence of strains resistant to two front-line drugs, INH and RIF (multi-drug-resistant TB), has been followed by the emergence of extended drug-resistant TB.⁶

Steroids are of proven benefit in reducing mortality and possibly morbidity in children.^{27,28} Hyponatremia is commonly seen and may be due to either the syndrome of inappropriate antidiuretic hormone (SIADH) secretion or cerebral salt wasting. Distinction between the two causes may be difficult; fluid restriction must be avoided unless there is clear evidence of fluid overload, and sodium replacement with hypertonic saline may be indicated.⁹ Follow-up imaging is of value in detecting complications, such as hydrocephalus and infarcts.²⁹



Fig. 80.1 Tuberculous meningitis. Axial computed tomographic scan following the intravenous administration of contrast showing hydrocephalus, low-density lesions in the basal ganglia, and leptomeningeal enhancement in the basal cisterns.

The optimal management of TBH is controversial with respect to the indications for surgery and the choice of operation, with most institutions developing their own treatment algorithms.³⁰ A logical point of departure is determining whether the patient has communicating hydrocephalus or noncommunicating hydrocephalus. Because axial CT is unreliable in this respect,³² a number of authors have advocated the use of air encephalography to demonstrate communication between the ventricular and subarachnoid CSF.^{18,33} This must be done under carefully controlled circumstances, with the option of immediate surgical intervention in cases of noncommunicating hydrocephalus.

Nonsurgical treatment will be effective in about 70% of children with communicating hydrocephalus. It entails the use of diuretics, such as acetazolamide (50 mg/kg) and furosemide,¹⁸ and/or repeated lumbar punctures.³⁴ Those who fail medical management will require a shunt. Bhagwati³⁵ reported the use of ventriculoatrial shunts in TBH in 1971, but ventriculoperitoneal shunts soon became the preferred option,³⁶ although various authors have reported a high rate of complications.^{37,38} Because some patients do not respond despite control of hydrocephalus, some authors advocate a selective approach, inserting an external ventricular drain as a temporary measure and then placing a shunt in those who respond.^{39,40}

Endoscopic third ventriculostomy (ETV) as a treatment option for noncommunicating hydrocephalus in acute TBH was first reported in 2003,⁴¹ and subsequent analysis of the experience at this center disclosed a success rate of about 60% in cases in which the procedure was successfully completed.³¹ ETV in

this setting is technically challenging because the floor of the third ventricle is usually thickened, and copious fibrinous exudate in the basal cisterns makes identification of the cisternal space and the major vessels difficult. Some authors report greater success with ETV in chronic TBH when the acute exudate has resolved.^{30,42}

With appropriate antituberculous therapy, the majority of children with TBM survive, but the long-term neurologic, psychometric, and behavioral outcome is often poor. A wide range of outcomes has been reported,¹⁸ with death in 7 to 57%, neurologic sequelae in 13 to 75%, and normal outcome in only 11 to 61%. There is an urgent need for improved diagnostic tools that will enable earlier diagnosis, as well as biological markers that reflect extent of disease and response to therapy.

80.1.2 Tuberculoma

Tuberculomas are discrete lesions that represent focal infection; multiple lesions may be present in half of all cases⁴³ and may be seen with or without concomitant TBM. In the preantibiotic era, tuberculomas accounted for 3.6 to 50.8% of intracranial masses encountered by neurosurgeons,⁴⁴ but these lesions have declined in neurosurgical importance since the advent of effective antituberculous drugs and modern imaging.

Tuberculomas can occur anywhere in the brain but are rare in the spinal cord.⁴⁵ They are found more commonly in children, in whom they have a predilection for the cerebellum. A tuberculoma most commonly comes to medical attention either as a large lesion with mass effect causing neurologic symptoms, hydrocephalus, or diagnostic uncertainty or as a smaller supratentorial lesion causing seizures.

A mature tuberculoma is typically a well-defined, lobulated, avascular mass with a yellowish, gritty, caseating central core surrounded by firm collagenous tissue or softer pink granulation tissue.⁴⁴ The wall tends to be thicker and more crenated or nodular than those of a typical bacterial abscess,⁴⁶ and the mass may be attached to adjacent dura, leading to the mistaken intraoperative impression of a meningioma. Immature lesions may consist of multiple small tubercles, some with caseating or cystic centers, and there may be intense white matter edema.⁴⁴ Microscopically, a central zone of necrosis is surrounded by tuberculous granulation tissue comprising epithelioid cells, Langerhans giant cells, lymphocytes, polymorphonuclear cells, and plasma cells; acid-fast bacilli are often identified.

The typical imaging appearance is a lesion that is isodense or hyperdense on CT and is isointense on T1 and hypointense on T2 MR imaging; T2 hypointensity is noteworthy because this is seldom found in other intracranial masses.^{47,48} Studies correlating the imaging appearance with pathology suggest that the most common type of necrosis seen in CNS tuberculomas is not caseous but gummatous necrosis, in which inflammatory granulation tissue undergoes ischemic necrosis. By contrast, caseous necrosis is hypodense or isodense on CT and is isointense or hypointense on T1 and hyperintense on T2 MR imaging (similar to a bacterial abscess).⁴⁶ The lesion enhances avidly with contrast, showing a dense unbroken ring of enhancement, in some cases an enhancing nodule or disk, or a combination of rings and disks, which may coalesce.⁴³

The clinical presentation is similar to that of other slowly evolving intracranial space-occupying lesions. Features that

may point to the diagnosis are constitutional symptoms (e.g., weight loss, fever, malaise); a history of TB or a TB contact; a high frequency of seizures, even with a cerebellar lesion; and a positive Mantoux test.⁴³ Young children may have macrocrania.

The old clinical observation that patients with tuberculomas are often better nourished than those with TBM may point to better immunologic function. Small lesions that present with seizures alone may be difficult to distinguish from cysticercal granulomas, and in the absence of active tuberculosis elsewhere, they may not require treatment other than anticonvulsants. This is discussed in more detail later in the chapter. Larger lesions should be treated with the standard four-drug regimen of INH, RIF, PZA, and either ethionamide or ethambutol for up to 4 months, followed by two drugs for up to 18 months or longer, depending on clinical and radiologic response.⁴⁹ Steroids may be indicated should there be significant edema, and anticonvulsants are often required.

Most tuberculomas resolve with medical treatment alone, and surgery is indicated only if the lesion causes life-threatening raised ICP or fails to respond to medical treatment, or if the diagnosis is in doubt. A clear plane of cleavage is typically found between the lesion and the brain,⁵⁰ and complete excision may be possible for lesions that are small enough or superficial (► Fig. 80.2). Larger lesions may require piecemeal removal, but this does carry a risk for inciting meningitis.⁴⁴ Stereotactic aspiration⁵¹ has been reported for deep-seated lesions, but this may be difficult owing to the firm nature of the lesions.⁴³ Hydrocephalus due to a posterior fossa lesion may be very effectively managed with an ETV (► Fig. 80.3). Despite appropriate and effective drug therapy, tuberculomas may sometimes enlarge,⁵² a phenomenon termed *paradoxical expansion*, but eventually most do respond.

80.1.3 Other Tuberculous Lesions

Tuberculous Abscess

Tuberculous abscess is an encapsulation of pus containing viable tubercle bacilli and must be distinguished from a tuberculoma with central liquefaction.⁵³ Tuberculous abscesses may be refractory to treatment despite repeated surgical drainage, and in one small series, the addition of thalidomide to the antituberculous treatment regimen resulted in significant improvement.⁵⁴ This effect is mediated via cytokines, such as TNF- α .⁴ Another immunologically mediated condition is the immune reconstitution inflammatory syndrome (IRIS) seen in HIV-infected patients following the commencement of combination antiretroviral therapy (cART).⁵⁵

Tuberculous Osteitis

Tuberculosis may on rare occasions involve the bones of the skull base or the vault (the lesions are often referred to as caries).⁵⁶ Tuberculous osteitis may present as a fluctuant scalp swelling (cold abscess) or as an ulcerated lesion that is easily mistaken for an infected scalp laceration. If the correct diagnosis is made, surgery may not be indicated because the lesion will usually respond to antituberculous drugs.

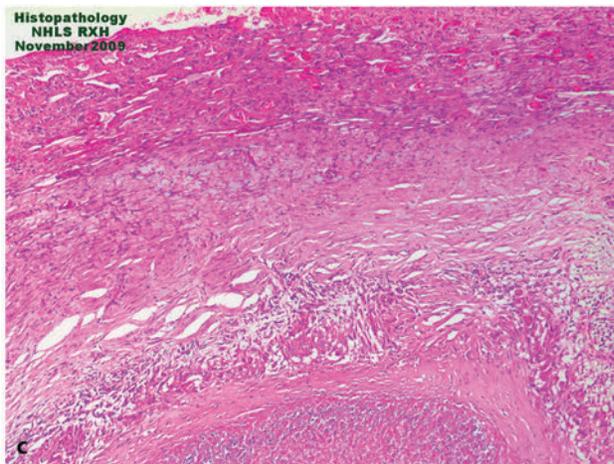
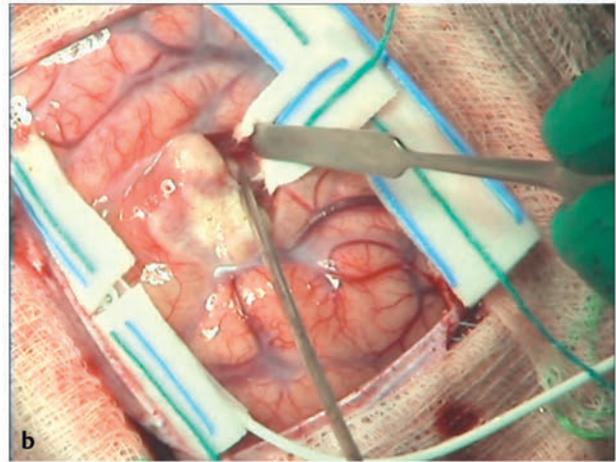
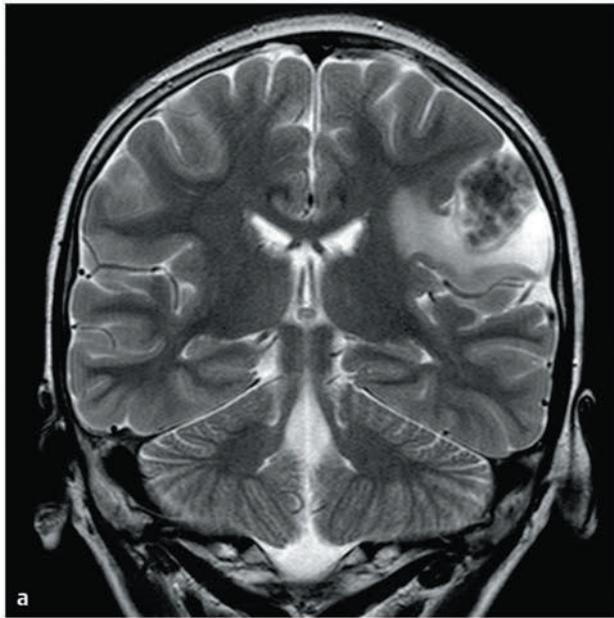


Fig. 80.2 Cortical tuberculoma. (a) A 12-year-old HIV-positive patient with a cortical lesion that did not respond despite 12 months of antituberculous treatment. Initial magnetic resonance image shows a T2 hypointense, inhomogeneous cortical tuberculoma in the left parietal lobe. (b) At surgery, the lesion was easily separated from the surrounding brain. (c) Histology showed typical features of a tuberculous granuloma.

Solitary Small Enhancing Cerebral Lesions

The small solitary cerebral lesion in a patient with seizures remains a subject of considerable interest. Although the differential diagnosis for a solitary cerebral enhancing lesion is extensive, the two most common inflammatory diagnoses, particularly in regions where they are endemic, remain tuberculosis and cysticercosis.⁵⁷ The relevant clinical and imaging features of these two conditions are summarized in ► Table 80.1. An Indian series comparing the features of these two inflammatory lesions listed some of the differentiating characteristics.⁵⁷ Active tuberculosis requires the commencement of antituberculous medication, whereas cysticercosis is usually self-limiting, requiring only single-agent antiepileptic medication with regular clinical and imaging follow-up to monitor resolution of the lesion.^{58,59}

80.2 Parasitic Infestations

Parasitic infestation of the CNS affects millions of people, mostly in the developing world, where poverty and related conditions prevail, although a change in the geographic distribution of these diseases has become more evident in the era of globalization. Parasitic infestations can be broadly classified as protozoan (caused by single-celled organisms) and metazoan/helminthic (caused by complex, multicellular organisms).

80.2.1 Cysticercosis

Cysticercosis was initially described by the ancient Greeks, who identified cysticerci (meaning “bladder tails”) in pork.⁶⁰ Neurocysticercosis results from infestation of the CNS by larvae of the helminthic tapeworm *Taenia solium*. Cysticercosis is the most

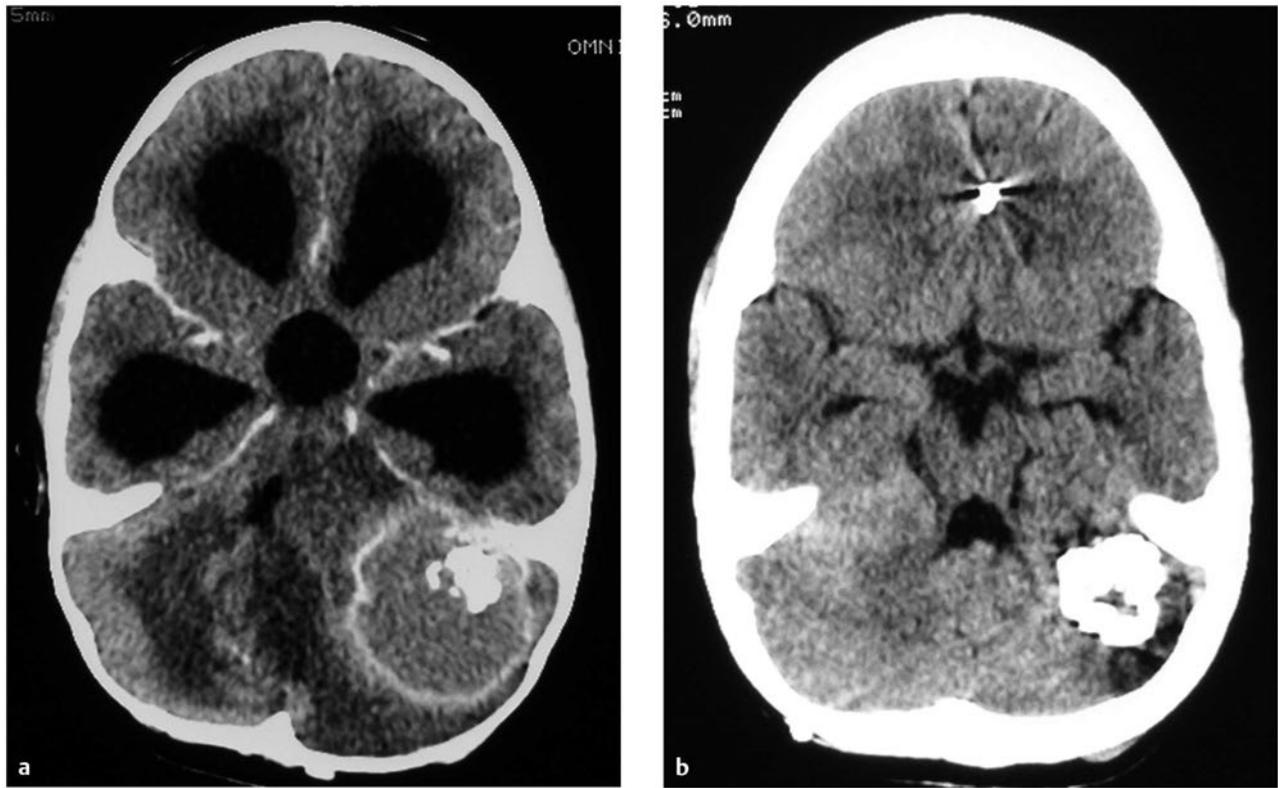


Fig. 80.3 Posterior fossa tuberculoma. (a) This patient presented with hydrocephalus, which was treated with a ventriculoperitoneal shunt, although our current practice is to consider an endoscopic third ventriculostomy. (b) The lesion responded well to antituberculous treatment.

common CNS parasitic infestation in humans and a leading cause of acquired epilepsy.⁶¹

Cysticercosis is widely endemic in those parts of the developing world where pork is consumed and sanitation is poor.⁶² *T. solium* infection is endemic in Central and South America and in non-Islamic regions of Asia and sub-Saharan Africa. In certain developed countries, the prevalence appears to be rising as a consequence of the increasing migrant workforce,^{63–65}

with some authors suggesting that the screening of potentially “at-risk” household employees be considered before employment.⁶⁶

The life cycle of *T. solium* involves pigs as intermediate hosts, after they ingest the eggs, and humans as definitive hosts, when they harbor the egg-producing adult tapeworm. The cycle is completed when a human inadvertently consumes mealy pork contaminated with viable *T. solium* eggs. The oncospheres enter

Table 80.1 Comparison of neurocysticercal and tuberculous lesions

	Neurocysticercal lesion	Tuberculous lesion
Number	Usually single, can be multiple	May be single or multiple
Location	Usually frontal and parietal lobes	Can occur supratentorially or infratentorially
Edema	Minimal, depends on phase of development, midline shift unusual	Extensive surrounding edema, often with midline shift
Size	Dimension < 20 mm	Dimension > 20 mm
Enhancement pattern	Usually ring-enhancing, may have central hyperdensity (scolex); calcification usually indicates inactive lesion	Heterogeneous enhancement
Clinical features	Usually presents with seizures, raised intracranial pressure or progressive neurologic deficit rare	Usually features of raised intracranial pressure and/or progressive neurologic deficit
Disease course	Usually self-limiting, may require antiepileptic drugs for seizure control	Antituberculous medication required for progressive disease
Systemic involvement	None	May have systemic or pulmonary tuberculosis

the mucosa of the small intestine, mature over a 2- or 3-month period, and then spread hematogenously, displaying a predilection for muscle, brain, and skin.⁶⁷ Humans may also be autoinfected, either externally (fecal-oral route) or internally (reverse peristalsis). Between 5 and 40% of adult carriers of *T. solium* will develop cysticercosis.⁶⁸

Once an oncosphere enters the brain parenchyma, it develops through four identifiable phases: (1) vesicular phase (viable cyst with minimal host response); (2) colloidal phase (rupture of a degenerating cyst into surrounding parenchyma, inciting a strong immune response); (3) granular-nodular phase (further degeneration, with formation of a nodular cyst); and (4) calcified phase (death and calcification of the cyst).⁶⁹

Immunocompromised patients appear more susceptible to multiple-organ involvement, with HIV coinfection in neurocysticercosis increasing the risk for basilar meningitis and the formation of giant cysts.^{70,71} The effect of HIV infection on the natural history of neurocysticercosis, however, remains unclear.⁷² Carpio et al⁷³ have proposed a useful classification for neurocysticercosis based on viability and location: active when the parasite is alive, transitional if it is degenerating, and inactive if the parasite is dead. Each of these categories can be subclassified as parenchymal or extraparenchymal (i.e., meningeal, intraventricular, and subarachnoid forms).^{73,74} Traditionally, the term *cysticercus cellulosae* is used to describe thin-walled, 3- to 20-mm cysts (containing scolices) occurring within the parenchyma, and *cysticercus racemosus* to describe larger, “grapelike” vesicles (without scolices), usually located in the basal cisterns, ventricles, or sylvian fissure.^{69,75}

The clinical manifestations of neurocysticercosis vary, depending on the number, size, location, and developmental stage of the cysticercal lesions, as well as the host immune response.⁷⁶ The most common clinical manifestations are seizures, headache, and focal neurologic deficits. The parenchymal form presents with seizures or focal neurologic deficits caused by direct compression. The meningeal form may present with signs of raised ICP that is due to widespread arachnoiditis and adhesions leading to hydrocephalus. Cranial nerve palsies may be caused by vasculitis or fibrous adhesions. The intraventricular or cisternal form presents mostly with raised ICP due to hydrocephalus resulting from the obstruction of CSF flow. This form tends to be rapidly progressive.⁷⁷ Rarer neurologic manifestations include neurocognitive impairment, altered mental state, brainstem dysfunction, strokelike symptoms, and extrapyramidal signs.⁵⁹

Diagnostic criteria based on objective clinical findings, imaging features, and immunologic and epidemiologic data have been proposed.⁷⁸ In a hospital-based setting, however, neuroimaging remains the mainstay, with a definitive diagnosis made on the basis of histopathologic evidence. Lateral X-rays of the thigh and calf, in suspected cases of cysticercosis, often demonstrate cigar-shaped calcifications and may be useful in confirming the diagnosis. CT scans in the active phase of the disease demonstrate hypodense lesions, which may be single or multiple and of varying size, containing a hyperdense mural nodule (► Fig. 80.4). Ring enhancement is suggestive of perilesional inflammation, and calcification, which denotes inactive, degenerated lesions, is present in 50% of cases. MR imaging is more sensitive in demonstrating smaller cysts within the ventricular and subarachnoid spaces as well as the various stages of

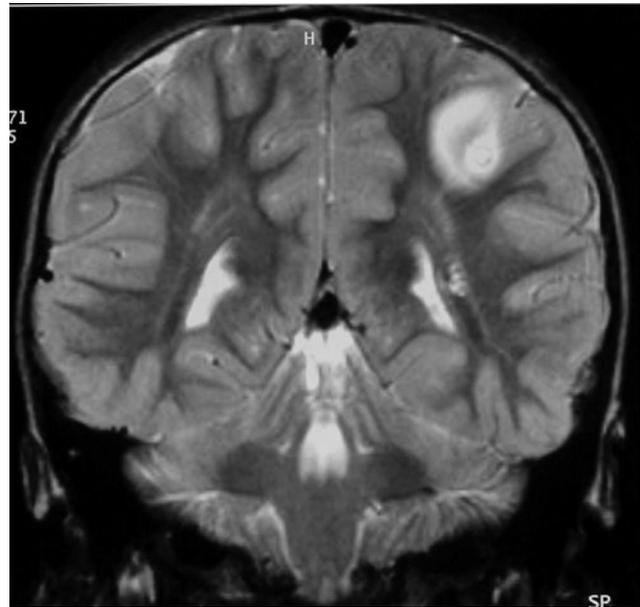


Fig. 80.4 Solitary neurocysticercus on T2 MR image (a) and anatomical pathology specimen (b) of an encysted cysticercus metacestode displaying a protoscolex. The germinal tissue forming the cyst wall is not marginated, consistent with viability and likely complete absence of contrast enhancement. (Courtesy of Dr. Richard Hewlett.)

development of the parasite. The cysts display distinctive features on both T1- and T2-weighted imaging.⁷⁹

Laboratory studies are useful in confirming the diagnosis. CSF mononuclear pleocytosis with raised protein and low glucose levels are typical findings in extraparenchymal disease, particularly with arachnoiditis.⁸⁰ Immunodiagnostic methods capable of detecting antibodies include complement fixation, indirect hemagglutination, enzyme-linked immunosorbent assay (ELISA), and enzyme-linked immunoelectrotransfer blot (EITB). ELISA and EITB are the most frequently used tests for the diagnosis of human cysticercosis, with EITB demonstrating 90% sensitivity for detecting human cysticercosis, but a much lower sensitivity for detecting single intracerebral lesions.⁸¹ In children with a single intracerebral lesion, EITB can yield false-negative results in 75% of cases.⁸² Serologic results, therefore, need to be interpreted together with clinical and radiologic findings.

The treatment modalities for neurocysticercosis include antiparasitic agents, symptomatic medication, and surgery. Guidelines proposed in 2002⁸³ suggest that there is insufficient evidence to support the recommendation of the antihelminthic drugs praziquantel and albendazole in neurocysticercosis and therefore recommend that treatment be individualized in terms of burden of disease and clinical presentation. Antihelminthic drugs are generally considered useful for long-term seizure control and for persisting or enlarging parenchymal lesions.⁸³ Albendazole appears superior to praziquantel because the latter has less efficacy for extraparenchymal lesions, interacts with steroids and antiepileptics, and may increase the risk for stroke.⁸⁴⁻⁸⁶ Antihelminthics should be used with caution in patients in whom raised ICP is suspected because the inflammatory response they evoke can precipitate further neurologic deterioration.

The use of corticosteroids in conjunction with antihelminthics is generally recommended because they reduce the inflammatory reaction caused by the death of the larvae and are beneficial in cases of cysticercotic encephalitis, as well as in cases with involvement of the meninges and subarachnoid space. Antiepileptic drugs remain the principal therapy for seizure control in neurocysticercosis.⁸³ Standard first-line antiepileptic drugs are usually adequate as single agents. The duration of treatment is controversial, however, and gradual cessation of the medication after resolution of the parasitic infection on imaging studies has been recommended.^{61–63} Standard treatment regimens appear effective in immunocompromised hosts, but the impact of antiretroviral therapy and immune reconstitution on the severity of the disease remains uncertain.⁷²

Neurosurgical intervention is indicated for (1) obtaining a tissue diagnosis, (2) relieving mass effect caused by the cyst, (3) treating raised ICP, (4) diverting the CSF to manage hydrocephalus, and (5) decompressing a compressed spinal cord and roots. A tissue diagnosis can be obtained via stereotactic biopsy or open craniotomy and resection of the lesion. Patients with neurocysts causing significant mass effect may require a craniotomy for adequate exposure and removal, and those with raised ICP due to hydrocephalus may require insertion of an external ventricular drain as a temporizing measure. Rates of ventriculoperitoneal shunt failure in neurocysticercosis are reportedly as high as 67%.⁸⁷ Endoscopic approaches have gained increasing popularity for removing ventricular neurocysts, either as stand-alone treatments or in combination with ETV to treat hydrocephalus.^{88,89} In this setting, ETV is most useful when there is a noninflammatory obstruction at the level of the aqueduct.⁹⁰

Patients with parenchymal forms of neurocysticercosis have a better prognosis than those with the extraparenchymal form, particularly when the latter causes hydrocephalus and arachnoiditis.⁹¹ The eradication of cysticercosis remains dependent on prevention, which requires improvement in human sanitation and the public health infrastructure. This disease remains a biological marker of poverty and social disparity.

80.2.2 Echinococcosis (Hydatid Disease)

Hydatid disease is caused by the cestode *Echinococcus*. The disease is prevalent worldwide but is endemic in the sheep- and cattle-raising areas of the world, particularly Latin America, Australia, Mediterranean countries, the Middle East, and India. The most common genus found in humans is *Echinococcus granulosus*, with *Echinococcus multilocularis* and *Echinococcus vogeli* seen rarely. The definitive hosts for *Echinococcus* are canines, such as dogs, wolves, and foxes.⁹² Humans inadvertently serve as intermediate hosts by ingesting food contaminated with dog feces containing viable parasite eggs. The eggs form oncospheres in the human intestine, penetrate the mucosa, and spread hematogenously to the liver (75%), lungs (15%), and brain (2%).^{93,94} They usually grow at a rate of 1 cm per year, but growth of 5 to 10 cm within the first year has been reported,⁹⁵ and the eggs are able to survive for many years. Although cerebral involvement is rare, the majority of cases of cystic hydatid disease, up to 75%, are found in children.^{96–98} Most cysts are single and unilocular and are located in the distribution of the middle cerebral artery, but they may also

occur infratentorially.⁹² Rupture of the cyst is uncommon but may occur spontaneously or as a result of trauma.

There is a wide spectrum of clinical presentations in cerebral hydatid disease, with the presentation depending on the number, size, and location of the cysts as well as on the host immune response. Most patients present with symptoms and signs of raised ICP (i.e., headache, nausea, vomiting, papilledema, and focal neurologic deficit). Seizures may occur but are uncommon.

Hydatid disease can be diagnosed in a patient with an appropriate history (resident in an area where the disease is endemic) based on the imaging and clinical findings, supported by serologic tests or the definitive identification of *E. granulosus* on histopathology. Serologic tests have a low sensitivity in cerebral hydatid disease, and characteristic imaging findings may still be diagnostic despite negative serology.^{92,93,99} Cerebral hydatid cysts appear as large, unilocular, thin-walled cysts, usually without calcification or surrounding edema, containing fluid with a density similar to that of CSF on CT scans and MR imaging (► Fig. 80.5). Calcification on a CT scan usually signifies death of the parasite, but areas of calcification and irregularity along the cyst wall may suggest previous rupture.¹⁰⁰

The treatment of cerebral hydatid disease remains primarily surgical,¹⁰¹ with antihelminthic therapy (benzimidazoles) given as adjunctive treatment for systemic disease, recurrence, or intraoperative rupture of a cyst.¹⁰² The goal is intact removal of the cyst without spillage of the contents. Dowling's technique,¹⁰³ in which hydrostatic dissection is used to define the plane between the delicate cyst wall and brain parenchyma, remains a popular method of in toto cyst extirpation. The surgical principles for removal of a cerebral hydatid cyst involve a large craniotomy, careful opening of the dura (particularly in the case of a superficially located cyst), and microsurgical dissection of the cortex with adequate exposure of the cyst wall. Fine-bore catheters are gently inserted between the cyst wall and cortex, and normal saline (0.9%) is used for hydrodissection of the cyst wall from the parenchyma; simultaneous adjustment of the position of the patient's head and mild Valsalva may gently encourage the cyst to emerge. The placement of swabs soaked in hypertonic (5%) saline around the area of the cyst is helpful in the event of spillage, but care must be taken to avoid excessive systemic absorption. Intraoperative ultrasound may be useful in defining the borders of the cyst, especially if it is deeply located. Watertight dural and skin closure is essential. Cyst rupture during surgery is almost inevitably associated with recurrence and is an indication for the commencement of antihelminthic therapy.¹⁰² Cyst aspiration has been described but should be considered only when intact removal of the cyst is not possible. Usually, the brain re-expands to a remarkable extent within months, but occasionally postoperative complications may be seen, such as subdural collections or porencephalic cysts, seizures, and transient neurologic deficits. Mass effect from the subdural collection or porencephalic cyst may require shunt placement.^{101,104}

Spinal hydatid disease in children is rare and may be either intradural or extradural, involving the vertebrae. In the latter case, intact removal is almost impossible, whereas laminectomy and intact cyst removal usually provide the best results for intradural cysts. The reported recurrence rate of spinal hydatid

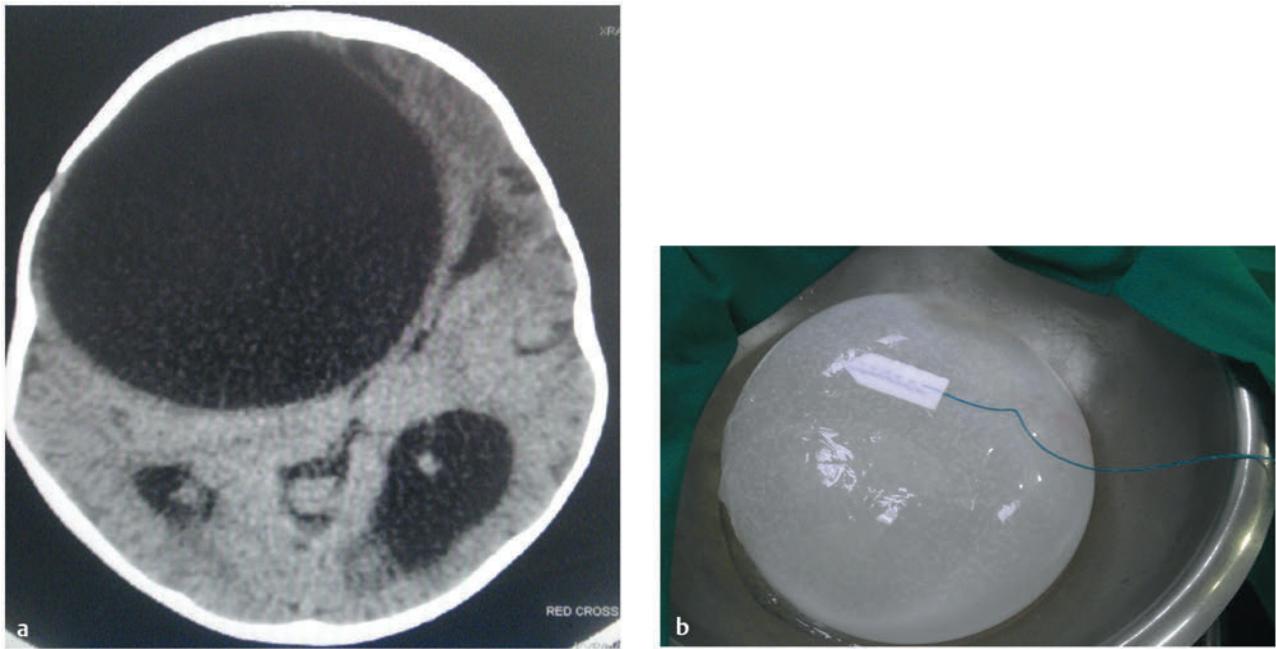


Fig. 80.5 (a) Very large frontal hydatid cyst seen on axial computed tomographic scan and (b) operative specimen following removal.

disease is about 40%, so careful clinical and imaging follow-up is necessary.^{105,106}

Hydatid cysts must be considered in the differential diagnosis of cystic lesions involving the CNS, particularly in regions where they are endemic. Early surgical treatment with intact cyst removal yields the best outcome.

80.2.3 Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan parasite, first recognized in the human retina in 1928.¹⁰⁷ Toxoplasmosis has a worldwide distribution. Felines are definitive hosts and excrete infectious feces, with humans and other mammals serving as intermediate hosts.

Toxoplasmosis in humans may be either acquired or congenital. The acquired form is associated with direct or insidious contact with cat feces, the consumption of contaminated fruit and vegetables, or the ingestion of oocytes in undercooked, contaminated meat. Congenital toxoplasmosis is transmitted during acute infection in pregnancy, with 1 per 1,000 pregnant women acquiring *T. gondii* infection during pregnancy.¹⁰⁸ The rate of fetal transmission is directly related to the gestational age at transmission, with the rate of transmission increasing with each trimester.¹⁰⁹ The increasing number of patients with immunocompromise, due either to HIV infection or to immunosuppression, has led to the emergence of toxoplasmosis as a potentially life-threatening opportunistic infection.¹¹⁰

The parasite invades the human intestine and multiplies; in the acute form of the infection, tachyzoites then disseminate hematogenously throughout the body. In CNS infection, diffuse involvement of the gray matter results in meningoencephalitis, with foci of perivascular inflammation.¹¹¹ Basal ganglionic and periventricular calcification has been reported in the fetus.¹¹² In congenital toxoplasmosis, hydrocephalus may result

from obstruction at the foramen of Monro or aqueduct of Sylvius. In immunocompromised hosts, widespread necrotizing lesions may occur within the CNS and other organs.¹¹³

The disease in children is classified as congenital, postnatally acquired, or ocular.

Congenital toxoplasmosis is often subclinical but may have a wide spectrum of clinical presentations, including the classic features of fever, hydrocephalus, chorioretinitis, cerebral calcification, seizures, microcephaly, and CSF abnormalities (markedly raised protein and mononuclear pleocytosis); systemic presentations, such as hepatosplenomegaly and jaundice, are also possible.^{114,115} The severity of the clinical disease in congenitally infected infants is inversely related to the gestational age at the time of maternal infection, with severe disease or death in 40 to 79% of fetuses infected in the first trimester, in 15 to 18% of fetuses infected in the second trimester, and in 0 to 3% of fetuses infected in the third trimester.¹⁰⁹ Congenital toxoplasmosis must be differentiated from other perinatal encephalopathies, which may coexist or present similarly. These include cytomegalovirus, herpes simplex virus, and rubella virus infections and certain metabolic and storage diseases.¹¹⁶

Acquired toxoplasmosis remains asymptomatic in most cases, with only 10 to 15% of patients exhibiting clinical symptoms and signs.¹¹⁶ In acquired toxoplasmosis involving the CNS, the predominant neurologic symptoms are headache, disorientation, and drowsiness, and toxoplasmosis should be considered in the differential diagnosis whenever evidence of acute CNS disease is noted.

Serologic tests remain the most common method of establishing the diagnosis. Fetal testing is indicated when *Toxoplasma* infection is identified either immediately before or during pregnancy. The detection of immunoglobulin M (IgM)-specific antibody in fetal blood or the isolation of *T. gondii* in amniotic fluid via cordocentesis or amniocentesis, respectively, has been used

to make the diagnosis of toxoplasmosis prenatally.^{117,118} Repeated fetal ultrasound demonstrates rapidly progressive, symmetric ventricular dilatation as the most common finding.¹¹⁹ When fetal toxoplasmosis is confirmed, antibiotic treatment with sulfadiazine and pyrimethamine together with folinic acid is recommended until delivery.¹¹⁶ A significant reduction in the severity of the clinical sequelae associated with congenital toxoplasmosis has been demonstrated with the use of spiramycin, pyrimethamine, and sulfonamides.¹²⁰ The diagnosis of congenital toxoplasmosis can be made through a combination of clinical examination, radiologic imaging, and CSF and serologic analysis, as well the isolation of *T. gondii* organisms from tissue or fluid specimens in acute infection (may take 4 to 6 weeks).

The postnatal treatment of congenital toxoplasmosis with pyrimethamine, sulfadiazine, folinic acid, and prednisone is recommended. Prednisone is indicated if the CSF protein is elevated or if sight-threatening chorioretinitis is present and is continued until either of these resolves.¹¹⁶ Untreated congenital toxoplasmosis carries a poor prognosis, but current treatment regimens, prolonged for 1 year, appear to substantially decrease the frequency and severity of neurologic sequelae.^{121,122} The coexistence of toxoplasmosis and HIV infection is rarer in children than in adults,¹²³ especially since the advent of HAART (highly active antiretroviral therapy). The treatment regimen with HIV infection, however, remains unchanged.

Hydrocephalus remains the condition most commonly associated with congenital toxoplasmosis and requires neurosurgical intervention. The pathogenesis of hydrocephalus in this setting is unclear, with studies suggesting both obstruction at the foramina and aqueduct of Sylvius and impaired absorption at the arachnoid villi as possible mechanisms.^{124,125} The nature of the hydrocephalus (i.e., obstructive or nonobstructive) has important implications regarding the options for treatment (ventriculoperitoneal shunt or ETV).

Toxoplasmosis of the CNS occurs in up to 40% of all HIV-infected patients and is the most common opportunistic infection to cause focal brain lesions.^{126,127} Acquired toxoplasmosis in children and adults is often asymptomatic. Three different neurologic patterns are evident in toxoplasmosis of the CNS: diffuse encephalitis with or without seizures, meningoencephalitis, and single or multiple mass lesions.¹²⁸

The diagnosis of toxoplasmosis of the CNS is based on a history of exposure and the presence of risk factors, the clinical examination, serologic and CSF testing (when lumbar puncture is safe), and radiologic features on CT and/or MR imaging. On radiologic imaging, cerebral toxoplasmic lesions often appear as multiple lesions (often more than five lesions), show ring enhancement with contrast, are typically located in the basal ganglia or at the gray–white matter interface, have minimal mass effect with mild edema, and often show evidence of cerebral atrophy.

As above, pyrimethamine, sulfadiazine, and folinic acid are recommended. Surgical intervention is reserved for biopsy in cases of diagnostic uncertainty, for the relief of mass effect, or for the prevention of impending herniation. The prognosis of patients with toxoplasmosis involving the CNS, particularly those who are immunocompromised, is poor. In a study of HIV-infected patients with toxoplasmosis of the CNS, fewer than half survived to 14 months after the initial diagnosis.^{129,130} Children with immunosuppression and acquired toxoplasmosis also have

high rates of mortality and neurologic sequelae.¹³¹ An early diagnosis and aggressive treatment are essential to obtaining the best possible outcome.

Prevention is vital in reducing both congenital and acquired toxoplasmosis. Pregnant women and immunosuppressed patients, and their families, should avoid contact with cat litter, cook meat to higher than 150°F, wash fruit and vegetables thoroughly, and clean cooking surfaces carefully. If seropositivity with a risk for congenital transmission is confirmed, treatment with antibiotic therapy should be initiated immediately.

80.2.4 Amebic Encephalitis

The first human cases of amebic encephalitis were reported in 1965 by Fowler and Carter.¹³² Free living amebae are found worldwide and thrive in warm, aquatic environments. Those causing CNS infection include *Balamuthia mandrillaris*, *Entamoeba histolytica*, and *Naegleria fowleri*. Amebic CNS involvement is rare but is almost always fatal. Primary amebic meningoencephalitis is typically caused by *N. fowleri*, with the other amebae usually causing a subacute or chronic form of infection known as granulomatous amebic encephalitis.

Patients who have primary amebic meningoencephalitis typically present with fever, severe headache, and symptoms of raised ICP within 2 weeks of exposure to contaminated water. Rapid progression to coma and death is the usual clinical scenario. Neuroimaging may be useful, but the definitive diagnosis is made via a wet mount of the CSF to detect motile trophozoites. The course in granulomatous amebic encephalitis is usually more protracted, lasting weeks to months, and the disease most commonly affects immunocompromised patients, often as an opportunistic infection in those with HIV infection.¹³³ The symptoms are nonspecific initially and evolve to altered mental status and focal neurologic deficit due to the space-occupying lesion. Patients generally progress to death within several weeks. Rapid diagnosis remains dependent on a detailed history looking for recent exposure to stagnant water bodies, a focused clinical examination, imaging features, and identification of the organism on wet smear.¹³⁴ Aggressive treatment strategies include antimicrobials, such as amphotericin B and metronidazole, with steroids and osmolar therapy as adjuncts in patients with raised ICP. Surgery may be necessary in cases with raised ICP and space-occupying lesions.

80.2.5 Schistosomiasis

Schistosomiasis is an infection caused by flukes of the genus *Schistosoma*. Three species—namely, *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*—lead to CNS involvement. Affecting up to 300 million people worldwide each year, schistosomiasis is the second most common parasitic infestation, after malaria, and is most frequently transmitted through contact with contaminated water bodies. Cerebral schistosomiasis typically manifests pathologically as space-occupying lesions, either single or multiple cerebral hemispheric lesions or nonspecific granulomas with surrounding edema.¹³⁵ The clinical presentation includes headache, altered mental state, seizures, and focal neurologic deficit, which usually commence weeks after the initial contact. CT or MR imaging usually demonstrates nodular, ring-enhancing intraparenchymal

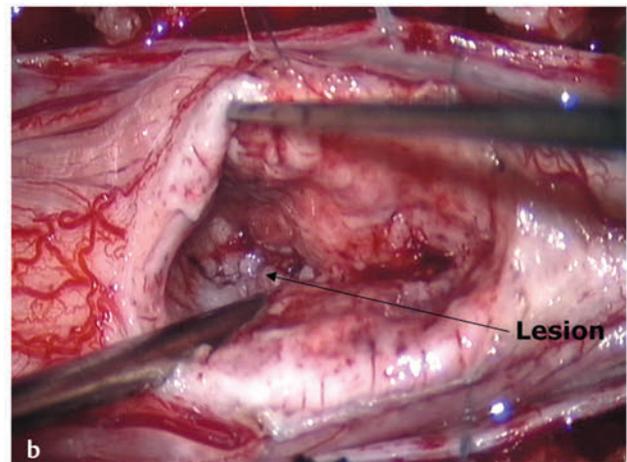


Fig. 80.6 A 10-year-old boy from East Africa was referred with progressive leg weakness and sphincter involvement. (a) Gadolinium-enhanced T1 magnetic resonance imaging showed an intramedullary mass thought to be a neoplasm, but (b) schistosomiasis was found following myelotomy.

lesions. Spinal cord infection, usually in the form of transverse myelitis, most frequently involves the conus medullaris or cauda equina.¹³⁶ Identification of the larva on a histopathologic specimen remains the gold standard for diagnosis (► Fig. 80.6). The antischistosomal drug praziquantel remains the mainstay of medical treatment. Surgical resection or biopsy may be required, depending on the size and location of the lesion.¹³⁷

80.2.6 Cerebral Malaria

Cerebral malaria is usually caused by infection with *Plasmodium falciparum* but rarely can be caused by *Plasmodium vivax*. Cerebral malaria, even with treatment and supportive care, has a reported mortality rate of 20 to 50%, the vast majority of fatalities occurring in African children.^{138,139} Fever is the clinical hallmark of cerebral malaria; other diagnostic features include coma, seizures, identification of *P. falciparum* or *P. vivax* on blood smear, and the exclusion of other causes of encephalopathy.¹⁴⁰ Management includes adequate resuscitation, supportive care, and the commencement of antimalarial treatment, the details of which fall beyond the scope of this chapter.

80.3 Fungal Infections

Fungi are ubiquitous in the environment but seldom pathogenic.¹⁴¹ Fungal invasion of the CNS generally produces one or more of the following pathologic scenarios: subacute or chronic meningitis, encephalitis, parenchymal brain abscesses or granulomas, and vasculitis or vascular thrombosis leading to ischemic injury. The diagnosis is usually made in a vulnerable patient with a history of exposure and is confirmed by serologic tests, CSF analysis, or histopathologic examination. Treatment with long-term courses of antifungal medication is usually required, and surgery for CSF diversion may be indicated in patients in whom hydrocephalus develops. Some of the more common CNS fungal infections are briefly discussed here, and ► Table 80.2 provides a more complete list.

Cryptococcosis is caused by *Cryptococcus neoformans*, an encapsulated yeast found worldwide. CNS infection with cryptococci is usually an opportunistic infection in immunocompromised patients. The clinical pattern is typical of meningitis, often with features of raised ICP. Laboratory diagnosis is usually made with India ink stain, but a serologic test (cryptococcal latex antigen test) is also available. Therapy usually includes amphotericin B with flucytosine (for 2 weeks), followed by oral

Table 80.2 Features of common fungal infections of the central nervous system

Fungal infection	Features
Cryptococcosis	Etiologic agent: <i>Cryptococcus neoformans</i> Found in pigeon droppings and soil Affects mainly immunocompromised patients Typically “pseudocysts” in the basal ganglia Raised intracranial pressure Meningitis ¹⁴²
Aspergillosis	Etiologic agents: <i>Aspergillus fumigatus</i> , <i>A. flavus</i> , <i>A. nidulans</i> , <i>A. niger</i> Angioinvasive, leading to arterial thrombosis Solitary or multiple abscesses, meningitis, granuloma, or mycotic aneurysms ^{141,143}
Candidiasis	Etiologic agents: <i>Candida albicans</i> , <i>C. glabrata</i> Less common: <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. krusei</i> Normal flora in mouth and gastrointestinal tract Low-birth-weight infants, critically ill patients, and surgical patients most at risk ¹⁴⁴ Meningitis and hydrocephalus
Histoplasmosis	Etiologic agent: <i>Histoplasma capsulatum</i> Found in soil contaminated with bird droppings Meningitis, encephalitis, multiple mass lesions of the brain or spinal cord ¹⁴¹
Blastomycosis	Etiologic agent: <i>Blastomyces dermatitidis</i> Found in moist soil Central nervous system involvement in 5 to 10% of patients with disseminated disease Meningitis, hydrocephalus, cerebral abscesses, or blastomycomas (granulomatous masses) ¹⁴¹
Coccidioidomycosis	Etiologic agent: <i>Coccidioides immitis</i> Found in soil Meningitis with secondary obstructive hydrocephalus, brain abscess ¹⁴⁵
Nocardiosis	Etiologic agent: <i>Nocardia asteroides</i> Usually affects immunocompromised patients Brain abscess

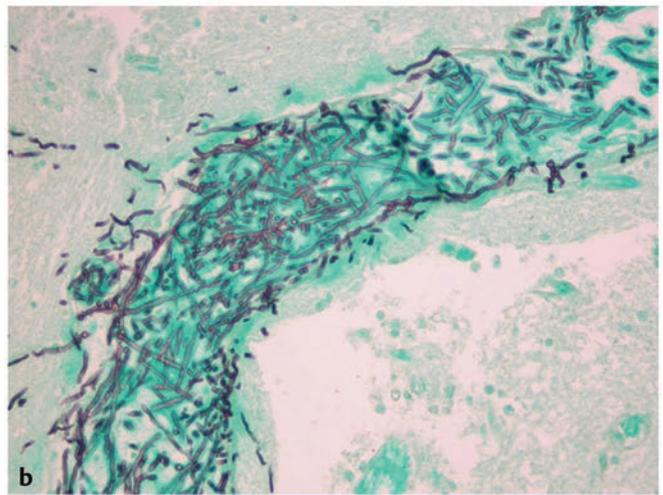
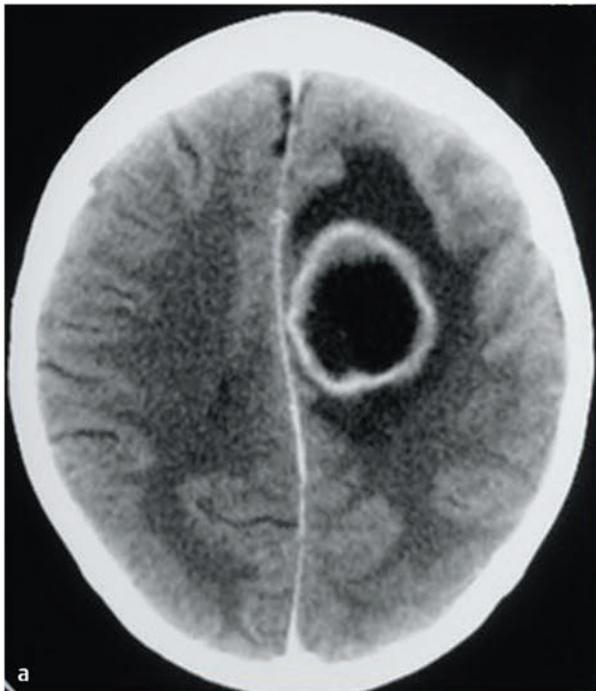


Fig. 80.7 One month after starting chemotherapy for leukemia, an 11-year-old boy developed a right hemiparesis. (a) Contrast-enhanced computed tomographic scan showed a ring-enhancing mass, which was excised. (b) Histology confirmed aspergillosis with evidence of vascular invasion on silver stain.

fluconazole for 8 weeks. Raised ICP can be managed with serial lumbar punctures, although a lumboperitoneal shunt may be required in patients in whom hydrocephalus develops.¹⁴²

CNS aspergillosis is usually caused by the organism *Aspergillus fumigatus*. Infection most commonly presents as an abscess and less commonly as meningitis. Excision of these lesions is recommended because they have a propensity for vascular invasion (► Fig. 80.7), which is followed by the formation of mycotic aneurysms. Combination therapy with the newer antifungal drugs and surgery has improved outcome.¹⁴³

Candida species are the most common pathogens in patients with end-stage AIDS. They often colonize central lines, external ventricular drains, and shunts. They can therefore either complicate the treatment of underlying hydrocephalus or be the causative organism.¹⁴⁴

Coccidioidomycosis, caused by the dimorphic fungus *Coccidioides immitis*, is endemic to semiarid regions. CNS infection is seen mostly in immunocompromised patients, usually with basal meningitis that often leads to hydrocephalus. Early shunt placement is often required, together with antifungal therapy.¹⁴⁵

Pearls

- Hyponatremia and imaging findings of basal meningeal enhancement, hypodense lesions in the basal ganglia, and hydrocephalus are common in TBM.
- Tuberculous vasculitis resulting in cerebral ischemia remains the most important cause of neurologic deterioration in TBM.
- Neurocysticercosis is a leading cause of acquired epilepsy.
- Hydatid disease must be borne in mind in the differential diagnosis for cystic lesions of the CNS, especially in areas where hydatid disease is endemic.
- Toxoplasmosis is the most common opportunistic infection causing focal brain lesions in patients infected with HIV.

80.4 Acknowledgments

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81 Infections of the Spinal Axis

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Infections of the spinal axis are an important although uncommon group of diseases that often present with insidious and variably progressive symptoms. The classic clinical hallmarks of infectious disease, such as fever, are variably present. Antimicrobial medical therapy constitutes the cornerstone of rational therapy if diagnosis occurs early. However, delay in diagnosis is common. Surgical intervention makes it possible to obtain tissue or fluid for microbiological diagnosis, drain localized abscesses, relieve compression of neurologic structures, or reconstruct segments of the bony spine destroyed by infection. With advances in imaging, antimicrobial chemotherapy, and the development of safe surgical methods of radical resection and reconstruction of collapsed vertebral segments, there exists the potential to treat and ameliorate the devastating morbidity and mortality that have long been associated with this group of diseases. Spinal infections in children are less completely characterized than those in adults because more of the medical literature consists of case reports and small case series.

81.1 Pyogenic Infections of the Spinal Axis

The pyogenic infections include infections of the vertebral bodies (spondylitis), facet joints (spondylitic arthropathies), intervertebral disks (spondylodiskitis), and epidural space (epidural abscess).^{1,2} Infections within the dura (subdural empyema, intraparenchymal spinal cord abscess) have been described but are vanishingly rare in the absence of a congenital dysraphic defect, such as a dermal sinus tract, or severe bacterial meningitis. In pyogenic infections, the offending bacteria elicit an inflammatory response that follows a usual acute phase inflammatory reaction (humoral immunity). As such, the predominant leukocytes in the region of inflammation are polymorphonuclear neutrophils. Large populations of lysed polymorphonuclear neutrophils and local necrotic tissue give rise to the purulence for which pyogenic infections are named. The offending bacteria are most commonly staphylococci and streptococci, but gram-negative organisms and *Propionibacterium acnes* have been identified and implicated.³ There has been a pronounced recent increase in the incidence of postoperative pyogenic infections with methicillin-resistant *Staphylococcus aureus* (MRSA).⁴ In at least one-third of cases, an offending organism is never identified. Unlike the microorganisms that cause pyogenic infections, acid-fast microorganisms (e.g., *Mycobacterium tuberculosis*) and fungi characteristically give rise to a chronic granulomatous type of inflammatory response.^{2,5}

81.1.1 Diskitis

Diskitis in children is a well-recognized although rare clinical entity that may characteristically present three to four times per year in a busy primary pediatric center.⁶ The disease occurs spontaneously in young children and involves inflammation of the intervertebral disk or cartilaginous vertebral end plate.^{7,8} Diskitis affects children of all ages, but its prevalence is highest

in children younger than 5 years of age.^{6,8} The incidence of diskitis rises again in adolescents for unknown reasons. Diskitis may occur at any spinal level, but case series indicate that lumbosacral disease occurs more commonly than thoracic disease, which occurs more commonly than cervical disease.⁸

The etiology of spontaneous diskitis is controversial because negative needle biopsy culture rates of 30 to 50% have been repeatedly demonstrated. Some cases of pediatric spontaneous diskitis have also been observed to resolve without treatment. These observations have prompted some centers to consider it a benign, self-limited process and to characterize childhood spontaneous diskitis as either sterile or infectious. However, the theory of an infectious etiology remains most widely held, in which diskitis results from the hematogenous spread of infection from a remote site, such as the urinary or respiratory tract.^{6,8} Alternative routes of infection in adults include iatrogenic inoculation during surgery or other invasive procedures and direct extension from adjacent infected tissues.⁹

Children are at greater risk than adults for the hematogenous spread of infection to the disk space. In children younger than 8 years, a robust network of vessels spans from the cartilaginous vertebral end plate to the annulus fibrosus.⁶ The nutrient artery of the central canal gives rise to vascular channels that perforate the vertebral end plates and terminate in the disk space. This network of terminal vessels provides a potential route of direct inoculation of the disk space.^{10,11} The vascular network gradually involutes, with development such that the vascularity is limited to the annulus fibrosus in older children. By adulthood, there is no vascular supply to the disk.^{7,10,11} The cartilaginous end plates of the vertebral bodies serve as an effective barrier to the transmission of infection from the disk space to the vertebral bodies.¹¹ As such, an infectious process beginning in the disk only rarely spreads to involve adjacent vertebrae. Despite resistance to infection from the disk space, the vertebral bodies remain subject to damage by bacterial enzymes and by increased stress caused by deformed and dysfunctional intervertebral disks. Persistent diskitis may result in destruction of the vertebral end plate and exposure of the vertebral body to infection.^{8,9,11}

Clinical Findings

Diskitis often presents with nonspecific symptoms.^{6,8,12} Young children or toddlers often present with a limp or a refusal to stand or walk.^{7,13} The lumbar region is exclusively affected in such children. The assessment can be difficult because young children in pain are often agitated, fearful, and marginally cooperative, and they rarely if ever clearly relate the character or localization of their pain. A toddler with diskitis may crawl normally but refuse to stand and will otherwise appear well. An older child or adolescent may demonstrate a limp or gait impairment.^{8,12,14} Back pain is the most frequent symptom. Children may describe pain in the hips, legs, or genitals. Dysphagia, neck stiffness, and torticollis may accompany diskitis of the cervical spine. Patients are often afebrile or have a low-grade fever and only rarely appear systemically ill. Vague constitutional

symptoms, such as fatigue, weight loss, and appetite changes, may be present but are nonspecific. Therefore, a high index of clinical suspicion for diskitis in any child presenting with low back pain and nonspecific constitutional symptoms expedites the diagnosis and prevents the morbidity that may accompany diagnostic delays.

Children with diskitis do not have neurologic deficits.⁶ Weakness, numbness, or incontinence suggests a compressive lesion, epidural empyema, or intradural infection.^{7,8} Tenderness to palpation around the infected level and spasm of adjacent muscles are common physical examination findings in diskitis.^{14,15} A useful diagnostic examination involves requesting the patient to pick up an object from the floor. Patients with lumbosacral diskitis typically will be unwilling to flex the spine and instead will squat (bend with the knees and ankles and keep the spine in a straight or extended position) to lower the body.¹³

Diagnostic Tests

Laboratory

The initial laboratory evaluation should include a complete blood cell count with differential (CBC), measurement of the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR), and blood cultures. If possible, blood cultures should be obtained before the initiation of antibiotic therapy.^{2,12,15,16}

The leukocyte count will often be either normal or slightly elevated. The ESR and CRP are usually slightly higher than normal. Blood cultures can identify the causative organism in as many as 50% of patients with diskitis. This aids in the selection of appropriate antibiotic therapy. If antibiotic therapy has already been initiated and the blood cultures are unrevealing, temporarily withholding antibiotics may be considered in patients who are not declining clinically. In patients with fevers, attempts should be made to collect cultures while the fever is present.^{6-8,12,14}

Radiology

Radiographs of the young child with diskitis (typically demonstrate narrowing of the disk space and may show mild end plate changes if they are obtained several weeks into the illness) (► Fig. 81.1).^{8,14,17} Plain spine radiographs can be highly useful in confirming diskitis and may show changes in up to 76% of patients with diskitis, but they are less often abnormal in cases of vertebral osteomyelitis (46%).¹⁶ Computed tomography (CT) provides a detailed demonstration of the bony changes that occur in response to disk space infection, which may be difficult to appreciate on plain radiographs.¹⁷ CT studies can be obtained relatively quickly, unlike magnetic resonance (MR) imaging, which younger children may be unable to tolerate without sedation.¹⁷

MR imaging provides the best definition of the disk and the paravertebral soft tissues and is particularly useful in separating diskitis from osteomyelitis of the vertebral body. Hypointensity within the vertebral body is characteristic on T1-weighted imaging, representing subchondral fibrosis and bone sclerosis. Hyperintensity may be seen in the disk space and paravertebral tissues on T2-weighted sequences, reflecting tissue edema. The administration of gadolinium can help to define the borders of the infectious process. During monitoring after the completion



Fig. 81.1 Diskitis. Two-year-old female who presented with a 2-week history of back pain, limping and fever. Post-contrast sagittal T1 image shows edema of the L4–5 disc and the adjacent vertebral

of therapy, the T1-weighted and T2-weighted changes may persist despite clearance of the infection.^{14,15,17}

Treatment

The treatment of diskitis is aimed at resolving the infection, eliminating pain, and preventing the development of a more serious infection, such as pyogenic vertebral osteomyelitis (PVO) or epidural abscess. This can be achieved with nonoperative therapy in almost all pediatric cases. Some centers consider diskitis a benign, self-limited process and provide only analgesia and immobilization while the patient is closely observed for progress. Most centers appear, however, to embrace an infectious etiology and an antimicrobial route of management. If an accurate microbiological diagnosis can be obtained via blood cultures, treatment should be initiated with targeted antibiotics. However, it is common that noninvasive testing fails to identify a causative organism. At that point, the clinical options include initiation of a trial of empiric antimicrobial therapy, image-guided (either CT or fluoroscopy) biopsy, or open surgical biopsy.⁹ Virtually all series recommend empiric treatment and the reservation of invasive procedures for cases that fail to respond to 7 to 10 days of intravenous antimicrobial treatment.

The most common offending organism in diskitis depends on the clinical setting. In children with diskitis, *Streptococcus* and *Staphylococcus* species are frequent. In adults, who typically acquire diskitis as a complication of disk surgery (1 to 2%

incidence after elective spinal disk surgery), *Staphylococcus* species predominate. Empiric treatment with a combination of third-generation cephalosporin and oxacillin/clindamycin has been advocated.^{14,16,18,19} Recommendations for the duration of treatment for diskitis vary widely, but there is general agreement that therapy should be initiated with intravenous antibiotics for approximately 7 to 10 days, followed by treatment with oral therapy for 2 to 3 weeks until the symptoms resolve and the CRP level normalizes.^{14,20} Immobilization may contribute to pain control and may be discontinued after the resolution of symptoms⁹ because instability is not a risk of isolated diskitis.

81.1.2 Pyogenic Vertebral Osteomyelitis/Pyogenic Spondylodiskitis

Although insufficiently treated diskitis may evolve to pyogenic vertebral osteomyelitis (PVO), distinct clinical patterns emerge in the spontaneous, de novo presentation of each disorder.^{2,24,25} Vertebral osteomyelitis may demonstrate an acute, subacute, or chronic course that varies with both the age of the patient and the identity of the infecting organism. The child with vertebral osteomyelitis is usually older (past the age of 8 years) and more ill-appearing, and the incidence of fever may be higher.² The incidence of vertebral osteomyelitis peaks in adolescence and again in the later adult years.^{16,24} About 2 to 7% of all cases of osteomyelitis involve the spine, and pyogenic infection is the most prevalent spondylitis.^{23,24} Estimates of incidence range from 0.5 to 2.4 per 100,000 overall, but the numbers separate significantly according to age.^{4,21} In persons younger than 20 years, the incidence is 0.3 per 100,000, but it rises sharply in late adulthood to 6.5 per 100,000.¹⁶ Overall, societal incidence rates are increasing, but this is largely due to an increase in the number of elderly patients who are living longer with a greater burden of partially compensated chronic disease.

Like diskitis, spinal osteomyelitis occurs following the hematogenous spread of microbial pathogens from a remote infectious source.^{1,4,24,26} Infections of the skin, urinary tract, and sinuses are the most frequently implicated, and the majority of spinal infections are preceded by infections elsewhere. Any level of the spine may be affected, but the lumbar region is most frequently involved.¹ The Batson venous plexus is implicated in hematogenous spread to the lumbar region from the bladder and pelvis.^{11,27} Iatrogenic direct inoculation during invasive procedures and spread from an adjacent infection (e.g., psoas abscess) are other mechanisms by which PVO may occur.^{1,22,24,28}

Clinical Findings

PVO is seen more often in older children and young adolescents.^{4,21,23} The initial presentation is usually nonspecific, and symptoms of pain surrounding the involved spinal level predominate.²⁵ Unlike patients with diskitis, those with vertebral osteomyelitis are more likely to present with fever and to appear systemically ill. If neurologic deficits are present, they are secondary to compression of the neural elements^{16,23,27,28} and warrant prompt, aggressive evaluation, imaging, and possible intervention.

Diagnostic Tests

Laboratory

The goals of the laboratory work-up should be the same as in diskitis: to identify and isolate the causative organism to guide therapy. Initial studies should include CBC with differential, ESR, CRP, and blood and urine cultures.^{21,23–25} The CBC often contains an elevated leukocyte count. The ESR and CRP are usually increased (sensitivity, 98 to 100%), and again, serial CRP measurements are useful for monitoring the response to therapy.^{16,22} Blood cultures (sensitivity, 58%; range, 30 to 78%) and biopsy may be indicated in suspected cases of vertebral osteomyelitis.^{15,16,21,24} If the blood cultures are negative, then an image-guided or open biopsy (sensitivity, 77%; range, 47 to 100%) may be indicated if there is no response to empiric treatment. Invasive procedures for diagnosis should not be undertaken until a thorough work-up has failed to identify a microbiological diagnosis and there has been no response to empiric therapy. If an invasive procedure is required, image-guided biopsy typically offers the least morbid option for directly obtaining a tissue sample.

Purified protein derivative (PPD) testing may be helpful but is imperfect in diagnosing tuberculosis (TB) as the cause of vertebral osteomyelitis. TB is a rare cause of osteomyelitis in developed regions. Many children in the developing world will have been immunized with bacille Calmette-Guérin (BCG), which is a vaccine against TB made from an attenuated strain of live bovine TB bacilli. If the presentation is subacute or the history includes exposure to TB or *Brucella* (via the consumption of unsterilized milk), then cultures for *Mycobacterium* and *Brucella* may be helpful.^{2,29} Specific serologic assays, including *Bartonella* species (“cat scratch”), are available and should be considered when exposure to cats is an element of the clinical history or if the results of other investigations have been negative despite clinical indications of PVO.³⁰

Radiology

Plain film radiographs may reveal focal areas of bony erosion early in the course of the illness (► Fig. 81.2). As the disease progresses, destruction of the vertebral body and, potentially, collapse become much more apparent.^{16,17,31} CT studies can further define the extent of bony erosion and destruction.^{15,17,31} MR imaging is useful to separate infections of the vertebral body from those that are limited to the intervertebral disk. MR imaging is more sensitive and specific than other modalities, with demonstrated sensitivity of 96% and specificity of 93% in the diagnosis of vertebral osteomyelitis.^{24,28,30} Vertebral hypointensity on T1-weighted and hyperintensity on T2-weighted sequences represent edema or purulent fluid in the bone marrow or intervertebral disk space. MR imaging, enhanced with the administration of gadolinium, is useful for identifying associated epidural or paravertebral abscesses.^{16,17}

Treatment

Long-term antimicrobial therapy with immobilization is the optimal treatment for osteomyelitis.^{1,16} Empiric treatment, initially with broad-spectrum coverage, is often justified if an organism cannot be identified noninvasively. If cultures

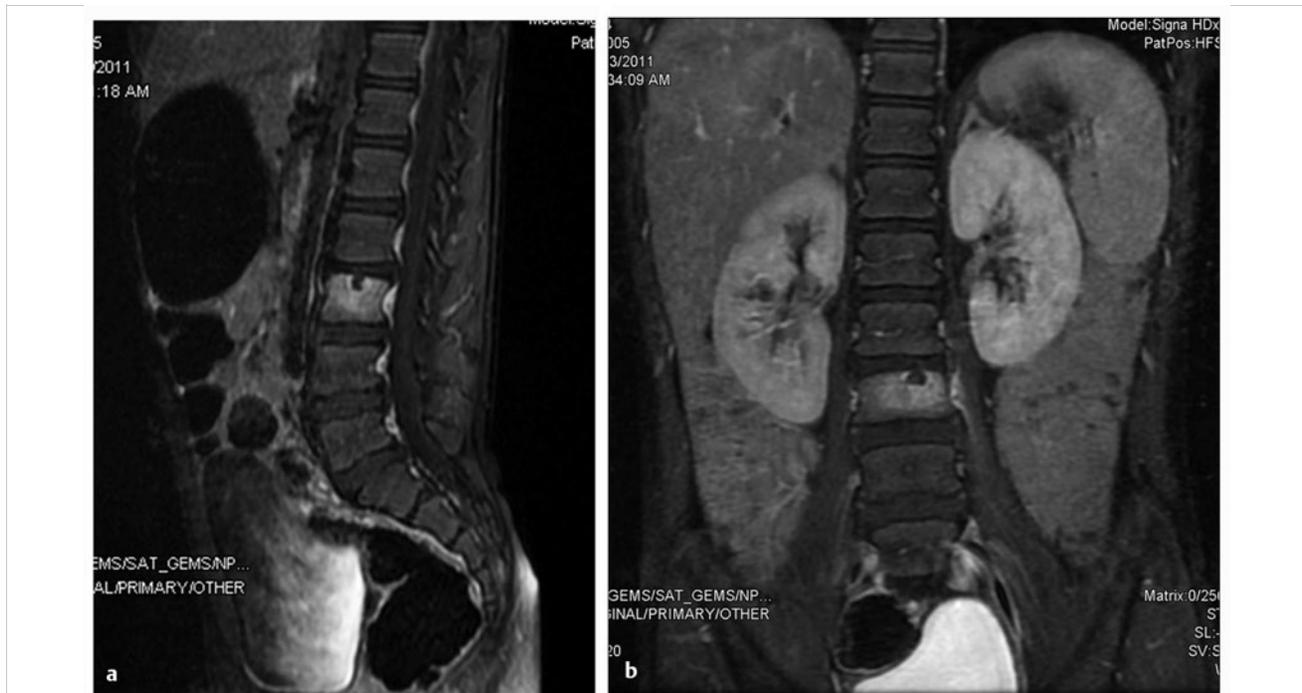


Fig. 81.2 (a,b) Pyogenic vertebral osteomyelitis. Six-year-old male had 2-week history of low back pain with sitting that resolves when lying down. There are no fevers. T1 post-contrast MRI discloses increased signal intensity within the L3 vertebral body with minimal signal change in the L2–3 disc. Blood cultures remained negative and patient did not respond to a 2-week course of IV Clindamycin. He was switched to Vancomycin and Rocephin with subsequent improvement.

obtained during the work-up reveal the causative organism, antibiotic treatment can be tailored appropriately. Current recommendations are for 6 weeks of intravenous antibiotic therapy with possible extension to 8 to 12 weeks depending on the relief of symptoms and reduction of the CRP and ESR.^{4,21,24,29}

81.1.3 Spinal Epidural Abscess

Epidural abscess was first described in 1761 and is recognized as a pyogenic infection of the epidural space. Spinal epidural abscess (SEA) may arise as a result of hematogenous seeding of the epidural space, of trauma or surgery, or of local extension of a soft-tissue abscess complicating PVO.³² It is now widely recognized that diskitis, PVO, and SEA may represent continuous points on a spectrum of infectious illness of the spine; however, the development of a SEA is a serious event that significantly increases the likelihood of permanent neurologic deficit.^{18,32} Neurologic injury may result from venous infarction due to local thrombophlebitis or from compression of the spinal cord or nerve roots caused by an inflammatory phlegmon.³³ The lumbar spine is preferentially involved. The diagnosis can be challenging because patients vary considerably in presentation.³⁴ An SEA may be a neurosurgical emergency, particularly in the setting of progressive neurologic deficit. However, the diagnosis of SEA is often delayed, and the neurologic deficit may be advanced and irreversible at the time of diagnosis. The reported

incidence of SEA ranges from 2 to 20 per 100,000, and the vast majority of cases occur in adults.^{32–34}

The majority of cases of SEA in children are individual case reports.^{18,35,36} SEAs in children are far less common than cranial epidural abscesses, which occur as a complication of common childhood illnesses, such as otitis media and sinusitis.^{37,38} In a 2001 review of SEA in children, Auletta and John noted that 26 pediatric patients with SEA had been reported in the medical literature, and they further characterized 8 children from their own institution. Most were boys without other illnesses, although 6 had concomitant PVO.³⁹ Observed similarities to adult SEAs were: rarity of the lesions, a prolonged symptomatic period before diagnosis, an etiology of hematogenous spread of infection, and easy detection with MR imaging. Important differences observed included an absence of predisposing conditions and less extensive abscesses in adults yet better outcomes in children.³² The location of the abscesses within the canal also differed significantly in that almost all pediatric SEAs were posterior, whereas a significant number of SEAs in adults were anterior.³⁹ Like the changes in the vascular anatomy of the disk space that impact the epidemiology of diskitis in adults and children, age-related differences in the vasculature of the epidural space may contribute to the preponderance of posteriorly located abscesses in children. These age-related changes in the vertebral vasculature may affect perfusion and the hematogenous distribution of infecting organisms.^{39,40}

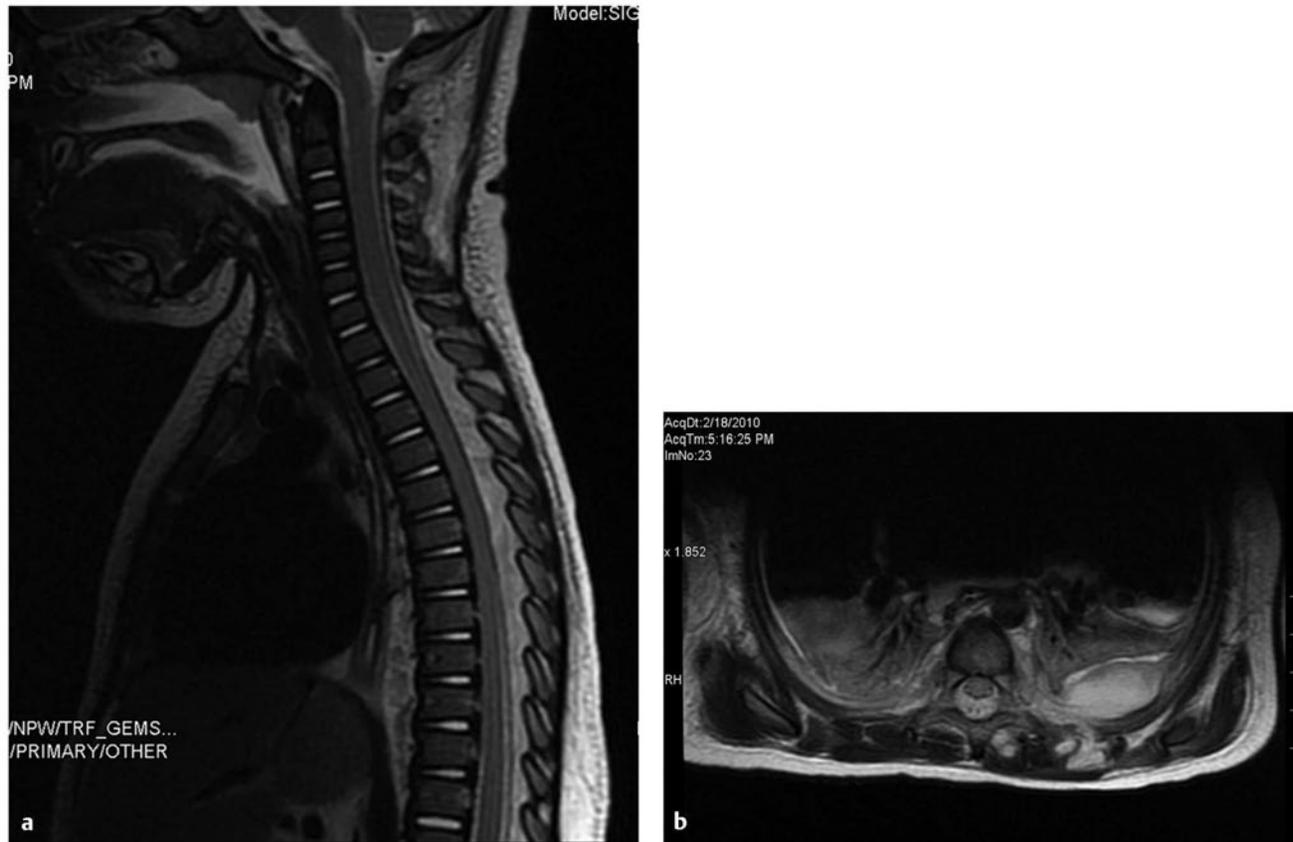


Fig. 81.3 (a,b) Spinal epidural abscess. T2 fat-suppressed MRI images of the spine in a 13-month-old female with MRSA sepsis and positive CSF cultures. There is a faint, dorsal epidural fluid collection from T1 through T9 with enhancement, a left pleural effusion, and paraspinal abscess. The patient was treated with 3 level laminoplasty with irrigation and debridement. She remained neurologically intact and resolved without sequelae.

Clinical Findings

The characteristic presentation of adults with the triad of progressive back pain, fever, and progressive neurologic deficit is widely reported in a minority of cases.³² In the large series of adult patients by Rigamonti and colleagues, 29% presented with limited or no back pain and no fever. Many patients had been seen multiple times before the diagnosis was made. Pain that was particularly sharp or lancinating and the presence of a neurologic deficit implicated SEA as more likely than PVO.⁴⁰ A meta-analysis of the comprehensive world literature identified 915 patients described with SEA. Most patients were in their mid 50s, but infants as young as 10 days old were described. Two-thirds of the patients had fever, and 71% reported back pain. Epidural catheters for regional anesthesia and spinal instrumentation were major iatrogenic sources of SEA.³²

Diagnostic Tests

Laboratory

Initial studies should include CBC with differential, ESR, CRP, and blood and urine cultures. As in PVO, the white cell count may be only minimally elevated (mean cell count, 15,000/mm³). The ESR and CRP are uniformly elevated in SEA.³² Culture data to guide antibiotic therapy can often be obtained by sampling during surgical decompression and evacuation.

Radiology

MR imaging is again the diagnostic modality of choice and is highly sensitive for SEA when performed with and without gadolinium contrast (► Fig. 81.3). Myelography via lumbar puncture is contraindicated because of the risk for seeding and secondarily infecting the subarachnoid space.

Treatment

Advances in imaging techniques, the development of highly effective antibiotic regimens, and advances in the understanding of spinal physiologic dynamics have fostered significantly better outcomes and prognosis for patients with SEA.³² Series from the 1950s and 1960s demonstrated combined rates of morbidity and mortality from SEA to be 34%, whereas those from the early 1990s showed that mortality had been halved, to 15%.^{32,33} Once an SEA is diagnosed, surgical intervention is virtually always indicated. Conservative management with antibiotics alone has been advocated in selected circumstances, but the possibility of sudden and irreversible neurologic decline despite antibiotic treatments warrants an aggressive surgical approach. In virtually all series, the best predictor of neurologic outcome in SEA is the patient's preoperative neurologic condition. A deficit that arises during antibiotic therapy and observation is unlikely to resolve. Situations in which surgical intervention might

not be appropriate include: 1) the presence of a very small amount of fluid in the epidural space (particularly if it extends over multiple levels) and no evidence of neurologic impairment, 2) the presence of complete neurologic deficit for longer than 3 days, 3) profound and overwhelming comorbidity adversely affecting the likelihood that the patient will survive an operation, and 4) refusal of the patient to consent to operative intervention.^{32,33,40}

Surgical goals include the evacuation of free pus from the epidural space, the sampling of infectious tissue to provide diagnostic cultures, and the maintenance and protection of spinal stability.^{34–36} In a patient with a free pyogenic infection, these goals can most often be accomplished via laminectomy. The purulent collection is almost uniformly posterior in all reported pediatric cases of SEA, but even when the collection is anterior, a laminectomy will often suffice to provide drainage and allow the sampling of material for diagnostic culture. Many SEAs involve multiple levels, and extended exposure is required to evacuate collections of pus. Surgical options include multiple-level laminectomies and alternating hemilaminotomies. An initial strategy incorporating alternating hemilaminotomies allows the surgeon to aspirate and vigorously irrigate the epidural space and still retain the posterior tension band that serves to prevent future slippage and the development of spondylolisthesis. If multiple-level hemilaminotomies (in which the spinous process and interspinous ligaments are spared) do not provide sufficient exposure to enable complete evacuation of the purulent material encountered in an SEA, then extension of the exposure to complete laminectomies can be undertaken at the surgeon's discretion. The use of surgical drains has not convincingly been shown to be superior to conventional closure alone.

The most common bacterial pathogens are *Staphylococcus* species—usually *S. aureus*. Non-iatrogenic (community-acquired) infections are usually broadly sensitive to methicillin (methicillin-sensitive *S. aureus*, or MSSA), whereas organisms resistant to methicillin (MRSA) are increasingly seen in situations of postoperative SEA. Antimicrobial chemotherapy should be administered at doses sufficient to achieve a tissue concentration adequate for elimination of the infection. Six weeks of intravenous antibiotics is usually considered the appropriate minimum duration of treatment. The course of recovery is monitored via the clinical signs (decreased pain and improved mobility) and laboratory values (normalized white blood cell count with decreasing CRP and/or ESR).^{33,34,40} Radiographic improvement is often delayed but can further document the regression and ultimate resolution of infection.

81.2 Granulomatous Infections

81.2.1 Tuberculosis of the Spine (Pott Disease)

Spinal TB (historically referred to as Pott disease after Percival Pott's classic description in 1786) occurs in approximately 1 to 3% of people who are infected with TB, yet the impact of tuberculous spondylodiskitis (TS) is immense because of the sheer number of people affected with TB.^{41–43} The prevalence of TB infection in the developing world is high, and a substantial resurgence of TB has occurred in the developed world in the last 30 years.⁴⁴ It is estimated that as many as 30 million people are

infected with TB throughout the world.⁴⁴ *M. tuberculosis* is transmitted via the inhalation of infectious particles and the establishment of pulmonary lesions. Hematogenous spread of microorganisms to the spine results in spinal tubercular osteomyelitis. Bovine TB (*Mycobacterium bovis*) is characteristically transmitted via the ingestion of tainted milk, so that the primary lesions are intestinal rather than pulmonary. Hematogenous spread is again implicated when *M. bovis* affects the spine.^{42,45} The axial skeleton is selectively but not exclusively involved and accounts for about 60% of all cases of tuberculous osteomyelitis.⁴² Typically, contiguous vertebral bodies and intervening disk spaces are affected. However, up to 10% of patients have multiple involved levels with intervening normal regions called skip lesions. There is a predilection for anterior vertebral body involvement of the thoracolumbar spine, although posterior elements may also be involved. Neurologic loss is observed in 10 to 40% of patients with TS.^{43,45,46}

In developed countries, public health initiatives and widespread effective antimicrobial regimens have significantly decreased the prevalence of TB (outside high-risk populations) and shifted the prevalence to adults. In the developing world, TS remains most common in the first three decades of life and is the leading cause of acquired paraplegia. Therefore, the epidemiology of spinal TB has evolved such that it is largely a disease of young persons in the developing world and nearly exclusively a disease of adults and the elderly in the developed world.^{46,47}

Although multiple classification systems have been proposed to characterize TS, the key distinctions are the formation of an epidural lesion, such as an abscess, granulation tissue, or a sequestrum, and whether the spine has been destabilized.^{41,43} Epidural masses, which are more common, may compress neurologic structures and adhere to the dura.^{48,49} Spinal cord injury occurs via either direct compression or venous infarction from local thrombophlebitis.

Direct invasion and destruction of a vertebral body is the other common pattern of TS and is the pattern most frequently seen in children. Such invasion leads to weakening of the bone, with the eventual compromise of columnar integrity and subsequent angulation and collapse. Severe kyphosis develops in about 3% of children with TS. Risk factors for severe deformity are young age (younger than 10 years), involvement of three or more vertebral bodies and a thoracic location.⁵⁰ Angulation may cause a point of focal compression where the spinal cord is draped over the apex. Irreversible myelopathic changes can occur subacutely or chronically. Spinal cord compression may also occur in the absence of collapse or epidural granulation when bony or cartilagenous sequestra formed as a result of bone infection and infarction is extruded into the spinal canal. The necrotic tissue becomes compressed and may be propelled laterally, anteriorly, or posteriorly into the spinal canal, with secondary compression of the adjacent thecal sac and spinal cord.⁴⁶

Clinical Findings

The presentation of TS depends upon the stage and form of the illness, which may differ significantly in developed and developing regions. In general, the initial presentation of TS reflects the status of the systemic illness, the bony insult, and the neurologic status.^{46,51} As with any infectious illness, there may be fever, diaphoresis (characteristically at night), secondary anorexia, and

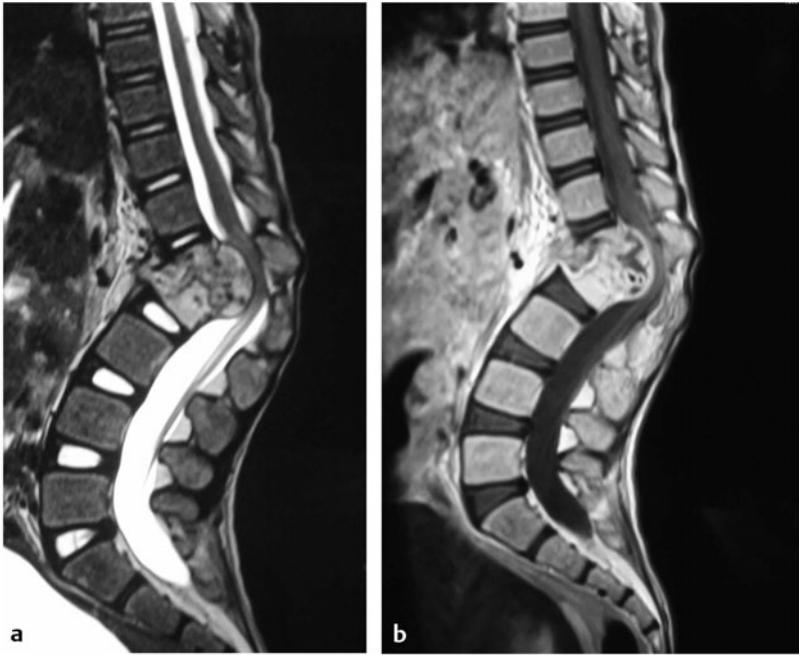


Fig. 81.4 (a,b) Lumbar spine tuberculosis. Eight-year-old, girl with chronic backache for last year. Physical examination: back deformity (low lumbar-dorsal kyphosis), painful on palpation, mild paraparesis 4-/5, sphincter dysfunction, hypotrophic lower limbs, hyperreflexia, and moderate spasticity. T1 and T2 MRI sequences reveal destruction of the vertebral body T12,L1,L2, respecting disk of T11 and L2, severe kyphoscoliosis with compression of the conus medullaris. There is a paravertebral abscess over both psoas. She went to surgery: laminectomy from T12, L1,L2, corpectomy of L1,L2 utilizing fibula as bone graft plus transpedicular screw placement in T11,T10 – L3,L4 plus rods and cross link. Previously, both paravertebral collections were evacuated to reveal caseum. Laboratory confirmed Koch bacille: Pott disease. (Case kindly provided by Dr. José Efraín García Reyes, Hospital Nacional Guillermo Almenara Irigoyen-Lima, Peru.)

weight loss.^{42,46} In children in developed regions, TS is rare and is associated with immune compromise, often presenting early in the course of the illness.^{45,52} Despite the early presentation, the diagnosis is often substantially delayed because of the lack of specificity of the presenting signs and symptoms. Clinical symptoms in children are characteristically insidious but may include back pain, malaise, and fever, in addition to neurologic decline in the form of paraparesis, sensory disturbance, or bowel and bladder dysfunction.^{41,45,48} Overall, neurologic involvement is reported in from 10 to 40% of cases but appears heavily weighted toward adults. Back pain is usually a predominant symptom, and for an experienced examiner, the degree of spasm and rigidity that accompany the pain is pathognomonic.^{45,49} In undeveloped regions, late presentation with a characteristic soft-tissue mass, a gibbus or kyphotic angulation, and a long history of back pain is more common.⁴⁵

Diagnostic Studies

Laboratory

Serologic investigation in active TB typically demonstrates a moderately elevated white blood cell count, an elevated ESR, and a mildly diminished hemoglobin concentration. Skin studies (Mantoux test) are often falsely negative if the patient is immunocompromised. Furthermore, BCG immunization, which is widely conducted in the developing world as vaccination for TB, has a success rate of approximately 80% in imparting immune resistance but uniformly causes a positive Mantoux test. The culture of acid-fast bacilli takes 6 to 8 weeks, but polymerase chain reaction specific for *Mycobacterium* DNA sequences is rapid and accurate when available.

Radiology

Plain radiographs first show disk space narrowing and end plate destruction, which may progress to anterior wedging or

vertebral angulation and collapse (► Fig. 81.4, ► Fig. 81.5). Pulmonary lesions may be demonstrated in 40 to 50% of cases, and spinal bony involvement is absent in 12 to 15%. MR imaging is now widely and rapidly available in developed countries and is the preferred examination. MR imaging characteristically demonstrates the full extent of TS, including epidural granulation tissue or abscess, adjacent soft tissue abscesses, and inflammation of the vertebral body or posterior elements. Characteristically, T1-weighted images show decreased signal from the affected marrow, decreased disk height, and involvement of the paraspinous soft tissue. T2 images show increased signal throughout the bone and adjacent soft tissue. A favorable response to treatment is best followed on T1-weighted images, on which an increase in signal intensity will be observed when images obtained after treatment are contrasted with previous images for the same patient.^{47,52}

In many developing countries, CT is the available imaging modality of choice. CT can quite adequately demonstrate the multiple manifestations of TS, including vertebral body compromise, paravertebral abscesses, and posterior element involvement, in addition to the extent of epidural involvement. Furthermore, CT may detect bone destruction earlier.³⁰

Treatment

The treatment and management of TS depend upon the presentation of the patient and must be individualized. If TS is diagnosed early, whereby the neurologic examination is intact and there is no bony destruction, then the patient is treated medically with or without immobilization. The greatest concern regarding conservative treatment is the real incidence of progressive kyphosis. The immobilization of patients not requiring surgical intervention is a controversial topic. Bed rest has known serious complications, but because of concern for vertebral collapse, physicians are reluctant to allow weight bearing in infected individuals.

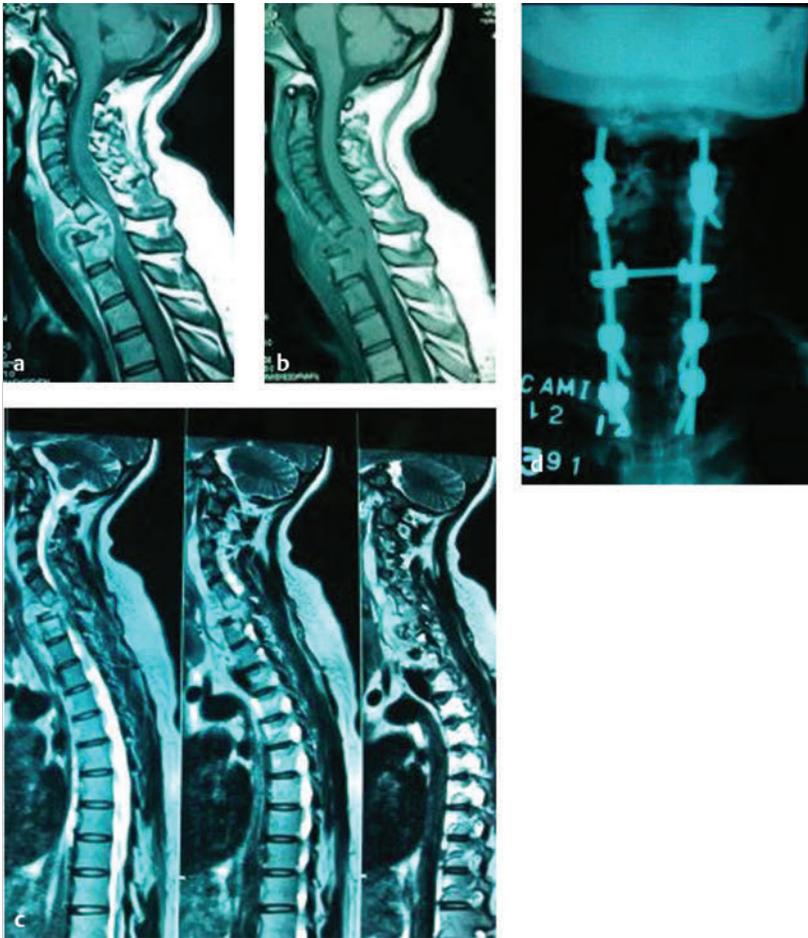


Fig. 81.5 (a–d) Cervical spine tuberculosis. Twenty-four-year-old male with neck pain, moderate quadriplegia, and loss of sphincter function. Contrast-enhanced sagittal MRI T1 sequences reveal destruction of C7 vertebral body with loss of vertebral height, retropulsion of inflammatory mass, cord compression, and kyphotic angulation. Surgical correction with vertebrectomy and multiple level posterior fusion. (Case kindly provided by Dr. José Efraín García Reyes, Hospital Nacional Guillermo Almendra Irigoyen-Lima, Peru.)

The Medical Research Council of England reported good results when antimicrobial chemotherapy was combined with ambulation in children. Medical treatment typically involves at least three agents for 6 months.^{46,53} Introduced in 1947, streptomycin was the first antimicrobial to show efficacy against acid-fast bacilli. A common regimen consists of rifampin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampin and isoniazid for a variable period of 7 to 9 additional months.⁵³

Various surgical approaches for TS have been debated in the medical literature.^{51,54,55} Limited surgery consists of laminectomy, whereas a more radical operation involves an anterior approach with complete resection of infected and compromised vertebral bodies and secondary reconstruction with a bone graft (the Hong Kong procedure).^{55,56} Several modifications to the Hong Kong procedure have recently been advocated that center on the incorporation of internal fixation with instrumentation.^{57,58} The two conceptually divergent approaches are antimicrobial chemotherapy (either with or without bed rest) and radical surgery (Hong Kong procedure or variant). The Medical Research Council of the United Kingdom addressed this controversy with a prospective study that demonstrated comparable rates of long-term disease control and eradication in the two treatment groups (85 and 89%, respectively) but reduced long-term deformity in the patients treated with radical surgery.⁵⁵

There appears to be consensus that surgery is indicated in the following situations: (1) there is neurologic compromise

that may be arrested, (2) kyphosis or angulation is progressive or severe, (3) pain is severe and associated with kyphosis or collapse, (4) there is evidence of progression of disease while the patient is on optimized medical therapy, and (5) the diagnosis is in doubt.^{54–56} It is recognized that children have a greater potential to develop kyphosis with growth over time.^{57,58} Surgical goals include the decompression of neural elements, stabilization of columnar spinal stability, and correction of any kyphosis that may be present.

Laminectomy is the preferred procedure when the primary problem is a dorsal epidural collection of granulation material and no kyphosis is present.⁵¹ Laminectomy is insufficient when the patient has significant vertebral body disease because of the potential for delayed kyphosis and the inability to address any ventral spinal cord compression that may be present. Posterior instrumented fusion can meaningfully augment stabilization but can do little to correct kyphosis. Instrumented fixation and stabilization can be undertaken in a field actively infected with TB without any apparent elevation in the risk for delayed infection.⁵¹

Vertebral body involvement at the time of diagnosis is common, and the presence of, or risk for, the development of kyphosis is central to guiding surgical decision making. An anterior decompression via a transthoracic, transpleural, or retroperitoneal approach that is augmented with a bone graft is highly effective at restoring sagittal balance, preventing further kyphosis, and protecting the spinal cord.^{55,56} Posterior instru-

mented fusion can be done at same time or in a staged fashion. More extensive surgery appears to be more effective in correcting the degree of deformity in children, but only a very limited experience in young children has been reported to date.^{55,56,58}

81.2.2 Tuberculosis of the Craniovertebral Arch

This rare variant of TS occurs frequently in developing countries, but infrequently in the developed world. It is associated with severe complications because of the involvement of ligaments at the craniocervical junction, with potential for ligamentous laxity and secondary instability. Atlantoaxial dislocation, translocation of the dens, and cervicomedullary compression have been described. The diagnosis is obtained on the basis of CT (or rarely MR imaging), which reveals subluxation of the C1–2 elements. Traction, immobilization, and antimicrobial therapy form the basis of treatment.⁵⁹

81.2.3 Brucellosis

In areas where it is endemic (South America, central Asia, the Middle East, and the Mediterranean region), brucellosis is a public health problem, and it is the most common zoonosis in humans.⁶⁰ The species most commonly seen are *Brucella abortus*, *Brucella melitensis*, and *Brucella suis*. All are intracellular pathogens. The incidence of systemic brucellosis is increasing, and 20 to 25% of cases involve children.⁶⁰ Transmission occurs from infected animals to humans via contact with body fluid (in adults) or the consumption of raw milk or milk products (in children). Cutaneous, hematologic, and respiratory complications are most common in children, whereas osteoarticular and cardiac complications are most frequent in adults.

Signs and symptoms are not specific and most commonly consist of arthralgia, fever, night sweats, and weight loss, but the disease can have a very wide clinical spectrum.⁶⁰ Spinal brucellosis resembles PVO and may be present focally or diffusely.²⁹ Focal disease occurs in the anterior end plate, whereas diffuse disease involves multiple levels and the intervening disk space. The diagnosis is based upon the identification of possible exposure, clinical features suggestive of brucellosis, and serologic tests with or without blood cultures. The sensitivity of serologic tests is 65 to 95%, but the specificity is low because of the presence of antibodies in the bloodstream in regions where brucellosis is endemic. Radiographically, there is characteristically sparing of the vertebral body and an absence of deformity.²⁹ Treatment requires at least two antibiotics (tetracycline, doxycycline, rifampin) for a duration of 6 weeks.

81.3 Conclusion

Infections of the spinal axis are an uncommon but important set of disorders that may be classified as pyogenic (acute humoral immunity) or granulomatous (chronic inflammation). Three patterns of pyogenic disease can be recognized: diskitis, vertebral osteomyelitis, and spinal epidural abscess. Diskitis does not compromise neurologic function, requires antibiotic treatment and immobilization, and has an excellent prognosis. Insufficiently treated or untreated diskitis may either resolve

spontaneously or go on to cause vertebral osteomyelitis or SEA. Vertebral osteomyelitis varies very widely in severity, carries a more serious prognosis, and requires prolonged antibiotic treatment. SEA threatens neurologic function via compression and local thrombophlebitis, which often lead to acute and irreversible deficits if timely surgical evacuation is not undertaken.

Infections that preferentially affect the vertebral body, such as tuberculosis, often compromise the integrity of the vertebral body and lead to kyphosis, deformity, and collapse. Any of these may acutely or chronically impair spinal cord function and cause permanent neurologic dysfunction. Surgery is indicated for a patient with severe or progressive kyphosis, neurologic decline, or disease progression while on appropriate medical therapy. Laminectomy, bracing, and antibiotics are just as effective as radical vertebrectomy with reconstruction for local disease control, but vertebrectomy is associated with better long-term correction of kyphosis and angulation.

Each of these entities presents challenges to timely diagnosis because of the insidious and nonspecific nature of the symptoms and the frequent presence of other important comorbid conditions. Therefore, a high index of awareness of these conditions will help the astute clinician avoid the delays in diagnosis and intervention that have been typical for this important group of illnesses.

Pearls

1. Diskitis must be suspected in any toddler who refuses to sit or stand. It is highly responsive to immobilization and a limited course of antibiotics.
2. PVO is characterized by a clinical appearance similar to that of diskitis, but the child appears sicker overall and has fever. Treatment with antibiotics for a minimum of 6 weeks is required, and both the clinical course and the laboratory values (CRP and ESR) must be followed to judge the duration of therapy. MR imaging allows a rapid, certain diagnosis and the initiation of therapy.
3. Tuberculous osteomyelitis is a disease of the young (first three decades) in the developing world and a disease of adults with significant comorbidities in developed regions.
4. Tuberculous osteomyelitis may compromise neurologic function via compression by an epidural mass or vertebral body collapse with angulation and kyphosis.
5. Surgical intervention for tuberculous osteomyelitis may be either via laminectomy with antibiotics and bracing or via anterior vertebrectomy and reconstruction. The two approaches do not differ in efficacy for local disease control, but vertebrectomy is associated with a reduced rate of complications related to kyphosis and angulation.

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Neuroanesthesia

82 Pediatric Neuroanesthesia

82 Pediatric Neuroanesthesia

Sulpicio G. Soriano and Mark A. Rockoff

Advances in pediatric neurosurgery and anesthetic techniques have dramatically improved the outcome in infants and children afflicted with surgical lesions of the central nervous system (CNS). However, the physiologic and developmental differences inherent in pediatric patients present challenges to neurosurgeons and anesthesiologists alike. The aim of this chapter is to highlight these age-dependent aspects of the perioperative management of the pediatric neurosurgical patient.

82.1 Developmental Considerations

Age-dependent differences in cerebrovascular physiology and cranial bone development have a significant impact on the perioperative management of neurosurgical patients. Cerebral blood flow is coupled tightly to metabolic demand, and both increase proportionally immediately after birth. Estimates from animal studies place the autoregulatory range of blood pressure in a normal newborn between 20 and 60 mm Hg.¹ This is consistent with the relatively low cerebral metabolic requirements and blood pressure during the perinatal period. Importantly, the slope of the autoregulatory curve drops and rises significantly at the lower and upper limits of the curve, respectively (► Fig. 82.1). This narrow range, with sudden hypotension and hypertension at either end of the autoregulatory curve, places the neonate, especially when premature, at risk for cerebral ischemia and intraventricular hemorrhage, respectively. Generally, full-term healthy infants have the ability to autoregulate their cerebral circulation, but premature neonates do not.² Furthermore, high-risk term and premature neonates do not exhibit intact cerebral autoregulation.³ Therefore, tight blood

pressure control is essential in the management of neonates to minimize both cerebral ischemia and intraventricular hemorrhage. On studies performed with noninvasive transcranial Doppler technology, the lower limits of cerebral autoregulation appear to be equivalent among older and younger children.⁴ However, children younger than 2 years old have lower baseline mean arterial pressures; they have less autoregulatory reserve and can theoretically be at greater risk for cerebral ischemia. Another developmental difference between an adult and a pediatric patient is the larger percentage of cardiac output that is directed to the brain in a child because the head of an infant or child accounts for a larger percentage of the body surface area and blood volume (► Fig. 82.2), resulting in proportionally greater blood loss and more significant hemodynamic instability in a small child than in an adult.

The infant's cranial vault is also in a state of development. The open fontanelles and cranial sutures result in a compliant intracranial space (► Fig. 82.3). The mass effect of a slow-growing tumor or insidious hemorrhage is often masked by a compensatory increase in intracranial volume accompanied by head growth. As a result, infants presenting with signs and symptoms of intracranial hypertension frequently have fairly advanced pathology. However, acute increases in cranial volume due to massive hemorrhage or an obstructed ventricular system will lead to life-threatening intracranial hypertension.⁵

Age-dependent variations also have pharmacologic and physiologic consequences for the perioperative course of neonates and infants. Total body water decreases from 85% in premature infants to 65% in adults, while body fat content increases from less than 1% in premature infants to 15% in term infants and 35% in adults. Total protein follows a similar trend. Therefore, hydrophilic drugs have more binding sites and hydrophobic

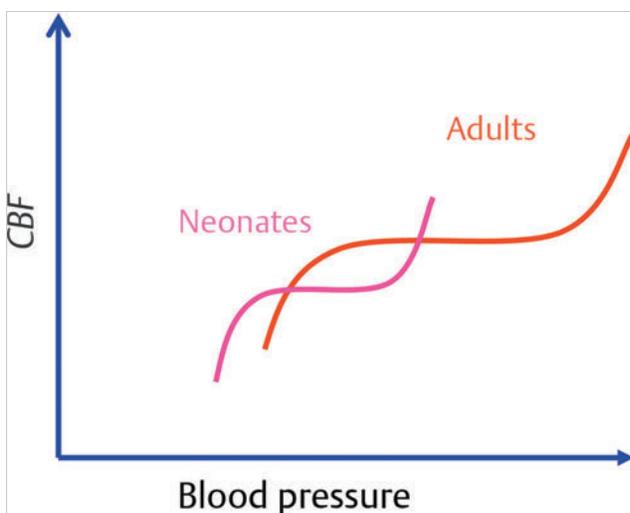


Fig. 82.1 Autoregulation of cerebral blood flow (CBF) in children. The slope of the autoregulatory curve drops and rises significantly at the lower and upper limits of the curve, respectively, and is shifted to the left in neonates and small children.

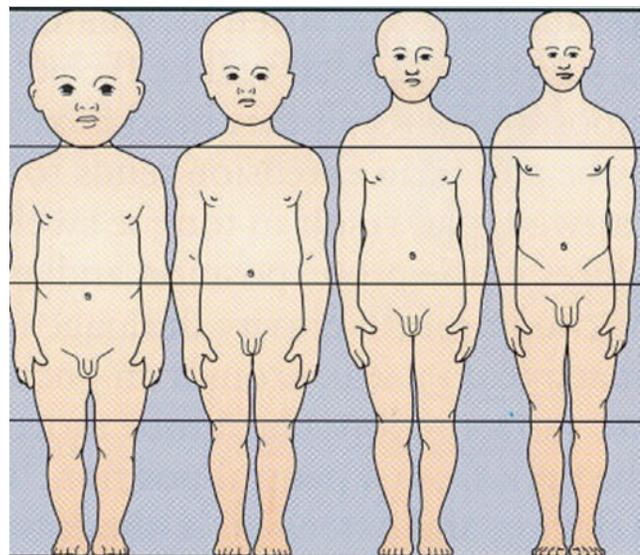


Fig. 82.2 Head size. The head size and surface area are proportionally greater in an infant than in an adult.

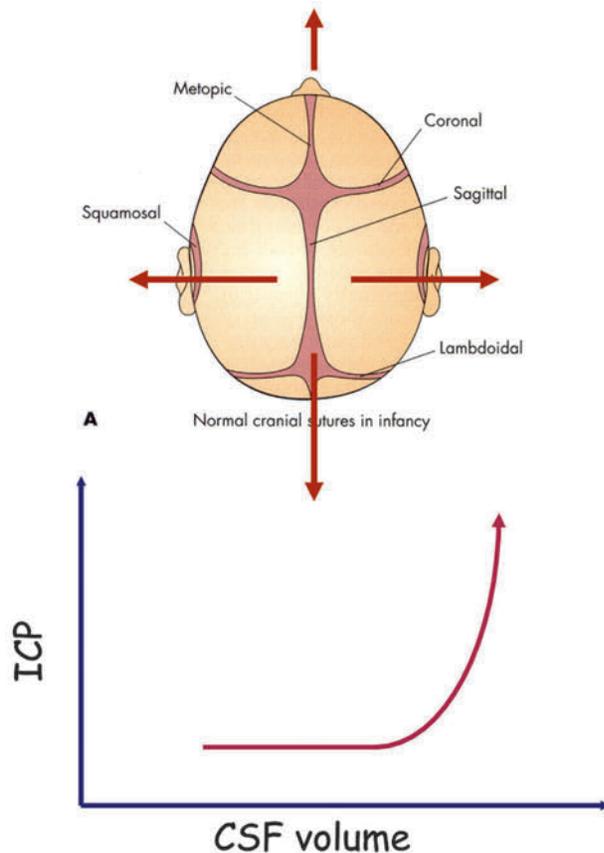


Fig. 82.3 (a,b) Effect of open cranial sutures and fontanel in neonates and infants. Initially, the compliant skull of the neonate will minimize insidious increases in intracranial volume. However, acute increases in intracranial volume (hemorrhage and obstructed ventriculoperitoneal shunt) will lead to rapid rises in intracranial pressure (ICP). CSF, cerebrospinal fluid.

drugs have fewer binding sites in infancy. The immature renal system is characterized by a decreased glomerular filtration rate and concentrating ability. These changes result in the diminished excretion of saline and water and limit the neonate's ability to compensate for fluctuations in fluid and solute loads. Furthermore, drugs that are excreted primarily in the urine may have a prolonged half-life. Hepatic function is also diminished in neonates, and the metabolism of drugs may be delayed because of the decreased activity of hepatic enzymes. The constellation of these factors should prompt the clinician generally to decrease the dose and frequency of administration of drugs given to the newborn.

82.2 Preoperative Evaluation and Preparation

Preparation of the pediatric patient for anesthesia and surgery is frequently overlooked in the perioperative period. Given the systemic effects of general anesthesia and the physiologic stress of surgery, an organ system review is essential for anticipating potential physiologic derangements and coexisting disease

Table 82.1 General perioperative concerns in infants and children

Condition	Anesthetic implications
Congenital heart disease	Hypoxia, arrhythmias, and cardiovascular instability. Paradoxical air emboli
Prematurity	Postoperative apnea
Gastrointestinal reflux	Aspiration pneumonia
Upper respiratory tract infection	Laryngospasm, bronchospasm, hypoxia, pneumonia
Craniofacial abnormality	Difficulty with airway management

states that may place the patient at increased risk for perioperative complications.⁶ General perioperative concerns in infants and children are listed in ► Table 82.1. Preoperative laboratory testing should be tailored to the proposed neurosurgical procedure. Given the risk for significant blood loss associated with surgery, a hematocrit in addition to prothrombin time and partial thromboplastin time tests, should be obtained to uncover any insidious hematologic disorder. Serum thyroid hormone levels should be obtained for patients with suprasellar pathology. Type- and cross-matched blood should be ordered before all craniotomies. ► Table 82.2 matches special concerns in pediatric patients with specific neurologic problems. Subspecialists in these areas may be needed to help optimize the patient's condition before surgery and to assist in postoperative management.

Closed-claim analysis studies have revealed that neonates and infants are at higher risk for morbidity and mortality than any other age group.^{7,8} Respiratory- and cardiac-related events account for a majority of these complications. However, no studies indicate any difference in the influence of neurosurgical disease on the morbidity and mortality of pediatric patients. Given the urgent nature of many pediatric neurosurgical procedures, a thorough preoperative evaluation may be difficult. However, a complete airway examination is essential because some craniofacial anomalies may require specialized techniques to secure the airway.⁹ Most cardiac morbidity due to congenital heart disease occurs during the first year of life. Congenital heart disease may not be apparent immediately after birth. Therefore, echocardiography can be helpful in the assessment of the cardiovascular system, especially in the neonate, and a pediatric cardiologist should evaluate a patient with suspected problems to help optimize cardiac function before surgery.

Anesthetic drug-induced neurotoxicity has been the focus of extensive preclinical and clinical research.¹⁰ It has been clearly demonstrated in fetal and neonatal laboratory animals that all classes of anesthetic drugs lead to a dose- and duration-dependent increase in neurodegeneration. However, retrospective epidemiologic reports have been inconclusive. Therefore, parents should be reassured that vital surgery cannot be performed without adequate anesthesia, and that the likelihood of the neurodegenerative effects of anesthetic drugs is insignificant in comparison with delaying or withholding anesthesia and surgery.

Separation from parents and perioperative anxiety play a significant role in the care of the pediatric neurosurgical patient. These issues are related to the cognitive development and age

Table 82.2 Common perioperative concerns for infants and children with neurologic problems

Condition	Anesthetic implications
Denervation injuries	Hyperkalemia after succinylcholine Resistance to nondepolarizing muscle relaxants Abnormal response to nerve stimulation
Chronic anticonvulsant therapy	Hepatic and hematologic abnormalities Increased metabolism of anesthetic agents
Arteriovenous malformation	Potential congestive heart failure
Neuromuscular disease	Malignant hyperthermia Respiratory failure Sudden cardiac death
Ketogenic diet and/or topiramate therapy	Chronic metabolic acidosis
Chiari malformation	Apnea Aspiration pneumonia
Hypothalamic/pituitary lesions	Diabetes insipidus Hypothyroidism Adrenal insufficiency

Table 82.3 Developmental factors affecting the pediatric patient in the perioperative period

Age group	Concerns
Infants (0 to 9 months)	None, will separate easily from parents
Preschoolers (9 months to 5 years)	Stranger anxiety, difficulty with parental separation
Grade-schoolers (6 to 12 years)	Fear of needles and pain
Adolescents (> 12 years)	Anxiety about surgery and self-image

of the child (► Table 82.3). Preoperative sedatives given before the induction of anesthesia can ease the transition from the preoperative holding area to the operating room.¹¹ Midazolam administered orally is particularly effective in relieving anxiety and producing amnesia. If an indwelling intravenous (IV) catheter is in place, midazolam can be slowly titrated to achieve sedation.

Preoperative fasting regimens have dramatically evolved over the years and vary according to local preferences.¹² The purpose of limiting oral intake is to minimize the risk for pulmonary aspiration of the gastric contents. However, prolonged fasting periods can result in both hypovolemia and hypoglycemia, which, in turn, can lead to hemodynamic and metabolic instability during anesthesia. Although the scientific validity of many recommendations has not been investigated, a common guideline is shown in ► Table 82.4.

82.3 Intraoperative Management

82.3.1 Induction of Anesthesia

The patient's neurologic status and coexisting abnormalities will dictate the appropriate technique and drugs for the induction of anesthesia. Often, general anesthesia can be established

Table 82.4 Common fasting guidelines for pediatric patients

Fasting time (h)	Oral intake
2	Clear liquids
4	Breast milk
6	Formula
8	Solid food

with the inhalation of sevoflurane and nitrous oxide with oxygen. A nondepolarizing muscle relaxant is then administered after IV access has been established to facilitate intubation of the trachea. Alternatively, if the patient already has an IV catheter, anesthesia can be induced with a sedative-hypnotic drug, such as propofol (3 to 4 mg/kg). These IV agents rapidly induce unconsciousness and can blunt the hemodynamic effects of tracheal intubation. Furthermore, they have minimal effects on cerebrovascular hemodynamics and maintain tight coupling of the cerebral blood flow and cerebral metabolic rate. Patients at risk for aspiration pneumonitis should undergo a rapid-sequence induction of anesthesia with propofol, immediately followed by the administration of a rapidly acting muscle relaxant and the application of cricoid pressure. Rocuronium can be used when succinylcholine is contraindicated, such as for patients with spinal cord injuries or paretic extremities. In these instances, succinylcholine can result in sudden, catastrophic hyperkalemia. Etomidate and ketamine are frequently used to induce anesthesia in hemodynamically compromised patients because these drugs are less likely to cause hypotension than is propofol. However, CNS excitation and increased intracranial pressure (ICP) have been associated with these drugs, respectively, and they may not be appropriate for some neurosurgical patients.

82.3.2 Airway Management

Developmental features of the airway anatomy have a significant impact on the management of the pediatric airway. The

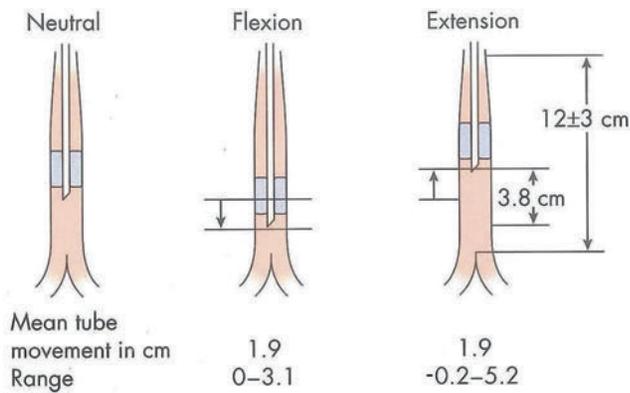


Fig. 82.4 Effect of head flexion and extension on endotracheal tube position.

infant's larynx is funnel-shaped and narrowest at the level of the cricoid ring. This feature places the infant at risk for subglottic obstruction secondary to mucosal swelling after prolonged endotracheal intubation with a tightly fitting endotracheal tube. Because the trachea is relatively short in the neonate and infant, an endotracheal tube can easily migrate into a main bronchus when the head is flexed, as is done during a suboccipital approach to the posterior fossa or the cervical spine (► Fig. 82.4). Therefore, great care should be devoted to ensuring proper positioning of the endotracheal tube during tracheal intubation, and the anesthesiologist should auscultate both lung fields to rule out inadvertent intubation of a main bronchus after final positioning of the patient for the procedure. Nasotracheal tubes are best suited for situations in which the patient will be prone.¹³ Furthermore, orotracheal tubes can kink at the base of the tongue when the head is flexed, resulting in airway obstruction and direct pressure injury to the tongue.

82.3.3 Positioning

Patient positioning for surgery requires careful preoperative planning to allow both the neurosurgeon and the anesthesiologist adequate access to the patient. ► Table 82.5 describes various surgical positions and their physiologic sequelae. The prone position is commonly used for posterior fossa and spinal cord surgery, although the sitting position may be more appropriate for obese patients, who may be difficult to ventilate in the prone position because of increased intra-abdominal pressure (► Fig. 82.5). In addition to the physiologic sequelae of this position, a whole spectrum of compression and stretch injuries have been reported. Padding under the chest and pelvis can support the torso. It is important to ensure free abdominal wall motion because increased intra-abdominal pressure can impair ventilation, cause vena caval compression, and increase epidural venous pressure and bleeding. Soft rolls are generally used to elevate and support the lateral chest wall and hips to minimize the increase in abdominal and thoracic pressure. In addition, they allow a Doppler probe to be placed on the chest without causing direct pressure injury. Many neurosurgical procedures are performed with the head slightly elevated to facilitate venous and cerebrospinal fluid (CSF) drainage from the surgical site. However, superior sagittal sinus pressure decreases with

Table 82.5 Physiologic effects of patient positioning

Position	Physiologic effect
Head elevated	Enhanced cerebral venous drainage Decreased cerebral blood flow Increased venous pooling in lower extremities Postural hypotension
Head down	Increased cerebral venous and intracranial pressure Decreased functional residual capacity (lung function) Decreased lung compliance
Prone	Venous congestion of face, tongue, and neck Decreased lung compliance Increased abdominal pressure possibly leading to vena caval compression
Lateral decubitus	Decreased compliance of downside lung



Fig. 82.5 Sitting position.

increasing head elevation; this increases the likelihood of venous air emboli (VAE).¹⁴ Extreme head flexion can cause brainstem compression in patients with posterior fossa pathology, such as mass lesions or a Chiari malformation. However, significant rotation of the head can impede venous return through the jugular veins and lead to impaired cerebral perfusion, increased ICP, and venous bleeding.

82.3.4 Vascular Access

Because of the limited access to the patient (especially small children) during neurosurgical procedures, ensuring optimal IV access is mandatory before the start of surgery. Typically, two large-bore venous cannulas are sufficient for most craniotomies. Should initial attempts fail, central venous cannulation may be necessary. Use of the femoral vein avoids the risk for pneumothorax associated with subclavian catheters and does not interfere with cerebral venous return, as may be the case with jugular catheters. Furthermore, femoral catheters are more easily accessible to the anesthesiologist during operations on the head. Because significant blood loss and hemodynamic instability can occur during craniotomies, cannulation of the radial artery provides direct blood pressure monitoring and

sampling for blood gas analysis. Other useful arterial sites in infants and children include the dorsalis pedis artery and posterior tibial artery.

82.3.5 Maintenance of Anesthesia

Several classes of drugs are used to maintain general anesthesia. Each has distinct characteristics that make it potentially appropriate for neurosurgery. Potent, volatile anesthetic agents (i.e., sevoflurane, isoflurane, and desflurane) are administered by inhalation. Sevoflurane has virtually replaced halothane as the principal agent for the induction of anesthesia in infants and children.¹⁵ It rapidly induces anesthesia and minimally depresses the cardiovascular system.¹⁶ Changing the inspired concentration of the drug can rapidly alter anesthetic depth. These inhaled drugs are potent cerebrovascular dilators and cerebral metabolic depressants, two qualities that can lead to a dose-dependent uncoupling of cerebral metabolic supply and demand and to increased cerebral blood volume and ICP. Moreover, their use can be associated with a significant decrease in cerebral perfusion pressure that is due primarily to a dose-dependent reduction in arterial blood pressure.¹⁷ Given these issues, volatile anesthetics are rarely used as the sole anesthetic for neurosurgery.

IV anesthetics are categorized as sedative-hypnotic or opioid. These drugs are also potent cerebral metabolic depressants but do not cause cerebral vasodilation. Therefore, they are closer to “ideal” anesthetics. Fentanyl is the opioid most commonly used in this setting. The context-sensitive half-life of fentanyl and sufentanil increase with repeated dosing or prolonged infusion, and the drugs require hepatic metabolism, which is immature in neonates. As a result, their narcotic effects, such as respiratory depression and sedation, may be prolonged. Remifentanyl is a unique opioid that is rapidly cleared by plasma esterases. Therefore, when administered at a rate of 0.2 to 1.0 $\mu\text{g}/\text{kg}$ per minute, it is an ideal opioid for rapid emergence from anesthesia.^{18,19} However, this rapid recovery is frequently accompanied by delirium and inadequate analgesia.^{20,21}

Nevertheless, the choice of agents for the maintenance of anesthesia has been shown not to affect the outcome of neurosurgical procedures when they are properly administered.²² The most frequently used anesthetic technique during neurosurgery consists of an opioid (fentanyl or remifentanyl) along with inhaled nitrous oxide (70%) and low-dose (0.2 to 0.5%) isoflurane. The incidence of awareness under anesthesia has been reported to be 0.8%, a value higher than that in adults.²³ Processed electroencephalographic algorithms have been advocated to measure the depth of anesthesia. However, their utility in children younger than 3 years is still in question.²⁴ Deep neuromuscular blockade with a nondepolarizing muscle relaxant is maintained to avoid patient movement and to minimize the amount of anesthetic agents needed. Patients receiving chronic anticonvulsant therapy will require larger doses of muscle relaxants and narcotics because of the induced enzymatic metabolism of these agents²⁵ (► Fig. 82.6). Muscle relaxants should be withheld or their effects permitted to wear off when an assessment of motor function during neurosurgery is planned.

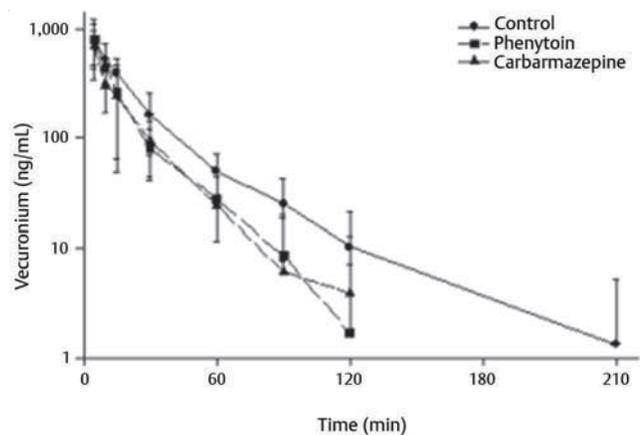


Fig. 82.6 Effect of chronic anticonvulsant therapy on the half-life of the muscle relaxant vecuronium. Vecuronium plasma concentrations are plotted against time after a single bolus dose of vecuronium ($0.15 \text{ mg} \cdot \text{kg}^{-1}$). Mean \pm standard deviation is plotted for all three groups.

Table 82.6 Estimated blood volume in children

Age	Estimated blood volume (mL/kg)
Preterm neonates	100
Full-term neonates	90
Children 1 year or younger	80
Children 1 to 12 years	75
Adolescents and adults	70

82.3.6 Intraoperative Fluid and Electrolyte Management

Hemodynamic stability during intracranial surgery requires the careful maintenance of intravascular volume and electrolytes. Preoperative fluid restriction and/or diuretic therapy may lead to blood pressure instability and even cardiovascular collapse if sudden blood loss occurs during surgery. Therefore, normovolemia should be maintained throughout the procedure. Estimation of the patient's blood volume is essential in determining the amount of allowable blood loss and when blood will need to be transfused. Blood volume depends on the age and size of the patient, as delineated in ► Table 82.6. Normal saline is commonly used as the maintenance fluid during neurosurgery because it is mildly hyperosmolar (308 mOsm/kg) and should minimize cerebral edema. However, rapid infusion of large quantities of normal saline ($>60 \text{ mL}/\text{kg}$) can be associated with hyperchloremic acidosis.²⁶ Given the relatively large blood volume of the neonate and infant, the maintenance rate of fluid administration depends on the weight of the patient (► Table 82.7). Because significant blood loss is likely to occur during most craniotomies in infants and children, the maximum allowable blood loss should be determined in advance to know when blood should be transfused. However, there are no guidelines

regarding the threshold for transfusing blood, and the decision to transfuse should be dictated by the type of surgery, the underlying medical condition of the patient, and the potential for additional blood loss both intra- and postoperatively. Hematocrits of 21 to 25% should increase consideration for blood transfusion. Packed red blood cells (10 mL/kg) will increase the hematocrit by 10%. Initially, lost blood should be replaced with 3 mL of normal saline for each 1 mL of blood lost or with a volume of colloid solution, such as 5% albumin, equal to the volume of blood lost. Depending on the extent and length of the surgical procedure and the exposure of vascular beds, additional fluid administration at 3 to 10 mL/kg per hour may be necessary. Because gluconeogenesis in neonates is underdeveloped, it may be necessary to add some glucose to the maintenance IV fluids for those who were receiving glucose infusions in the preoperative period. However, surgery elicits a stress response, and children are generally able to maintain normal serum glucose levels without exogenous glucose administration.²⁷ In any case, hyperglycemia is always best avoided because it may exacerbate neurologic injury if ischemia occurs.

Brain swelling can be initially managed with hyperventilation and elevation of the head above the heart. Should these maneuvers fail, mannitol can be given IV at a dose of 0.25 to 1.0 g/kg. This will transiently alter the cerebral hemodynamics and raise the serum osmolality by 10 to 20 mOsm/kg.²⁸ However, repeated dosing can lead to extreme hyperosmolality, renal failure, and brain edema.²⁹ Furosemide is a useful adjunct to mannitol in decreasing acute cerebral edema and has been shown in vitro to prevent rebound swelling due to mannitol.^{29,30} All diuretics will interfere with the ability to use the urine output as a guide to the intravascular volume status.

82.3.7 Monitoring

Patients undergoing major craniotomies and spine surgery are at risk for sudden hemodynamic instability due to hemorrhage, VAE, herniation syndromes, and/or manipulation of the

cranial nerves. The potential for cerebral hypoperfusion generally warrants placement of an arterial cannula for continuous blood pressure monitoring and access for sampling serial blood gases, electrolytes, glucose levels, and hematocrit. Although it may initially appear counterintuitive, small patient size decreases the threshold for inserting an arterial catheter because small children cannot tolerate as much blood loss as adults can.

The utility of central venous catheterization remains controversial. In adults, cannulation of the jugular or subclavian veins with catheters that have multiple orifices is often preferred, particularly when VAE are anticipated. However, these catheters are too large for infants and most small children. Furthermore, the central venous pressure may not accurately reflect intravascular volume in small children, particularly when they are in the prone position. Therefore, the risks of a central venous catheter may outweigh the benefits. In infants, even when VAE occur, the use of a central venous catheter for aspirating air is not frequently successful, presumably because of the high resistance of the small-gauge catheters placed in these patients.³¹

VAE have been detected during many craniotomies in infants and children, primarily because the head of a small child is large in relation to the rest of body and rests above the heart when the child is in either the prone or supine position (► Fig. 82.7).^{32,33} Standard neurosurgical techniques may elevate the patient's head even further by raising the head of the table to improve cerebral venous drainage. This maneuver can increase the risk for air entrainment into the venous system through open venous channels in bone and sinuses.¹⁴ Patients with cardiac defects and the potential for right-to-left shunting, such as those with a patent foramen ovale or patent ductus arteriosus, are at risk for paradoxical air emboli leading to potential cerebral or myocardial infarction. A precordial Doppler ultrasound device can detect minute VAE and should be routinely used in conjunction with an end-tidal carbon dioxide analyzer and arterial catheter in all craniotomies to detect VAE early, before significant hemodynamic instability develops. The Doppler probe is best positioned on the anterior chest, usually just over or to the right of the sternum at the fourth intercostal space (i.e., the nipple line). An alternate site on the posterior thorax can be used in infants weighing approximately 6 kg or less who are in the prone position.³⁴ In addition to the characteristic changes in Doppler sounds, sudden decreases in end-tidal CO₂, dysrhythmias, and/or ischemic changes in the electrocardiogram can occur with VAE.

Table 82.7 Rate of maintenance of fluid administration

Weight (kg)	Rate
≤ 10	4 mL/kg/h
10–20	40 mL + 2 mL/kg/h for every kg > 10 kg
≥ 20	60 mL + 1 mL/kg/h for every kg > 20 kg

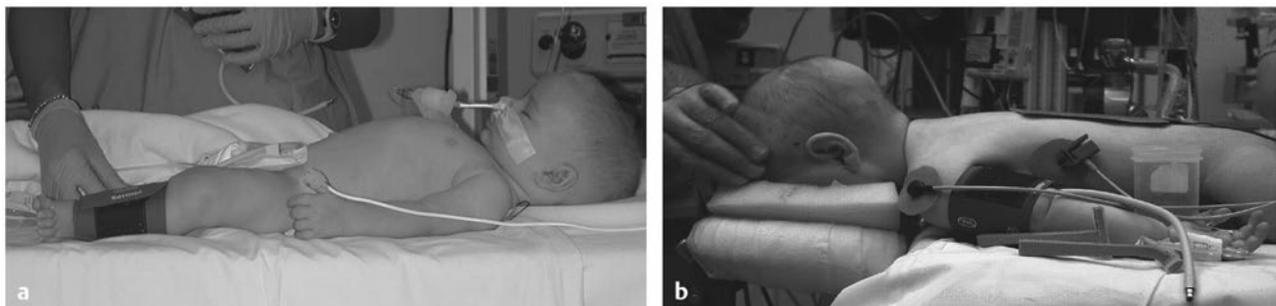


Fig. 82.7 (a) Supine and (b) prone infant. Note that the infant's head lies at a higher plane than the rest of his body. This increases the likelihood for venous air embolism during craniotomies.

Table 82.8 Anesthetic agents and their effects on various neurophysiologic monitors

	MAP	CBF	CPP	ICP	CMRO ₂	SSEP/MEP amplitude	SSEP/MEP latency
Inhaled agents							
Halothane	↓↓	↑↑↑	↑↑	↑↑	↓↓	↓	↑
Isoflurane	↓↓	↑	↑↑	↑	↓↓↓	↓	↑
Sevoflurane	↓↓	↑	↑	∅ – ↑	↓↓↓	↓	↑
Desflurane	↓↓	↑	↑	↑	↓	↓	↑
Nitrous oxide	∅ – ↓	↑ – ↑↑	↓	↑ – ↑↑	↓↑	↓	∅ – ↑
IV agents							
Thiopental	↓↓	↓↓↓	↑↑↑	↓↓↓	↓↓↓	↓	↑
Propofol	↓↓↓	↓↓↓	↑↑	↓↓	↓↓↓	↑	↑
Etomidate	∅ – ↓	↓↓↓	↑↑	↓↓↓	↓↓↓	↑	↑
Ketamine	↑↑	↑↑↑	↓	↑↑↑	↑	↑	∅
Midazolam	∅ – ↓	↓↓	↑	∅	↓↓	↓	∅ – ↑
Fentanyl	∅ – ↓	↓	↓↑	∅ – ↓	↓	↓	↑
Dexmedetomidine	∅ – ↑	↓	↓↑	∅ – ↓	↓	↓	↑

Abbreviations: CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate of oxygen; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; MEP, motor evoked potential; SSEP, somatosensory evoked potential.

Neurophysiologic Monitoring

Recent advances in neurophysiologic monitoring have enhanced the ability to perform more definitive neurosurgical resections safely in functional areas of the brain and spinal cord. However, the depressant effects of many anesthetic agents limit the utility of these monitors. A major part of preoperative planning should include a thorough discussion of the modality and type of neurophysiologic monitoring to be used during any surgical procedure. In general, electrocorticography (ECoG) and electroencephalography (EEG) can be used when levels of volatile anesthetics are low. Somatosensory evoked potentials (SSEPs), used during spinal and brainstem surgery, can also be depressed by high levels of volatile agents and, to a lesser extent, nitrous oxide. An opioid-based anesthetic is the most appropriate agent for this type of monitoring. Spinal cord and peripheral nerve surgery may require electromyography (EMG) and the detection of muscle movement as an end point. Therefore, muscle relaxation should be either avoided or permitted to dissipate during the monitoring period. ▶ Table 82.8 lists common anesthetic agents and their effects on various neurophysiologic monitors.

Monitoring of Cerebral Oxygenation

The primary cause of cerebral ischemia in infants and children is cerebral hypoperfusion secondary to systemic arterial hypotension, especially when it is accompanied by intracranial hypertension. The three potential clinical intraoperative modalities for monitoring cerebral ischemia are (1) EEG, (2) transcranial Doppler, and (3) near-infrared spectroscopy. However, during the routine use of these monitoring modalities, technical difficulties with positioning and recording are frequently encountered because of the proximity of the surgery. Clinical

studies have yet to demonstrate any clinical improvement with their use in the intraoperative setting.

Detection of Seizure Foci

Recent advances in neurophysiologic monitoring have enhanced the ability to perform more definitive neurosurgical resections safely in functional areas of the brain and spinal cord. However, the depressant effects of many anesthetic agents limit the utility of these monitors. A major part of preoperative planning should include a thorough discussion of the modality and type of neurophysiologic monitoring to be used during the surgical procedure. In ECoG, grid and strip electrodes are placed on the surface of the brain following dural opening. Because some epileptogenic foci are in close proximity to cortical areas controlling speech, memory, and motor or sensory function, monitoring of the patient's electrophysiologic responses is frequently used to minimize iatrogenic injury to these areas.^{35–37} The detection of cortical stimulation of the motor strip in a child under general anesthesia will require either EMG or the direct visualization of muscle movement. Neuromuscular blockade should not be used in this situation. Cortical stimulation is possible with a dual-channel stimulator. Epileptogenic activity may be evidenced by clearly documented electrographic seizures or EEG spike activity, which consists of either interictal spikes of 50 to 80 milliseconds or sharp waves of 80 to 200 milliseconds. During anesthesia, the use of low concentrations of volatile anesthetics or nitrous oxide and opioids alone should avoid the attenuation of ECoG and EEG signals.

Monitoring in Awake Craniotomy

Neural function is best assessed in an awake and cooperative patient.³⁸ Positioning of the patient is critical for the success of

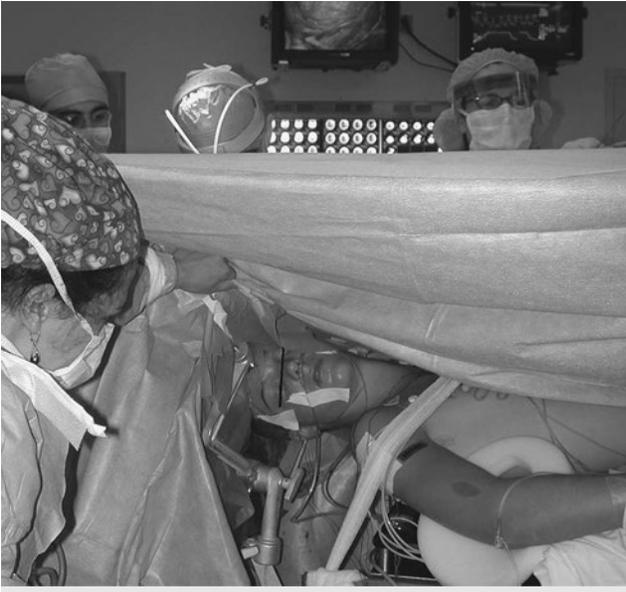


Fig. 82.8 Positioning the patient for an awake craniotomy. Note that there is clear access to the patient to facilitate neuropsychological testing.

this technique. A semilateral position allows both patient comfort and surgical and airway access to the patient (► Fig. 82.8). Motor and sensory regions of the cortex are localized by inducing motor movements or sensory changes with cortical stimulation. Language function is tested by eliciting speech arrest with cortical stimulation. Verbal memory is tested by stimulating the hippocampus or lateral temporal cortex. In a series of children undergoing awake craniotomy, in which local anesthesia and propofol and fentanyl or dexmedetomidine were used for sedation and analgesia during the resection of eloquent areas of the brain, we found that propofol, when discontinued 20 minutes before monitoring, did not interfere with ECoG, and cooperative children older than 10 years were able to withstand the procedure without incident.³⁹ However, it is imperative that candidates for an awake craniotomy be mature and psychologically prepared to participate in this procedure. Therefore, an awake craniotomy should not be considered appropriate for patients who are developmentally delayed or have a history of severe anxiety or psychiatric disorders. Very young patients cannot be expected to cooperate during these procedures and usually require general anesthesia with extensive neurophysiologic monitoring to minimize inadvertent resection of the eloquent cortex.

Monitoring Spinal Cord and Nerve Root Integrity

Surgery on the central neural axis exposes the patient to spinal cord injury or ischemia and nerve root damage. The instrumentation and surgical resection of spinal cord lesions risk damage to the spinal cord and nerve roots not only by direct injury but also by compromise of the arterial supply of the cord. Furthermore, brainstem surgery places vital nuclei and spinal pathways at risk for ischemia and direct damage. Monitoring SSEPs and performing an intraoperative wake-up test help detect these possible complications during surgery. Assessing motor evoked potentials (MEPs) may be helpful as well.

Somatosensory Evoked Potentials

SSEPs monitor primarily the integrity of the dorsal (sensory) pathways of the spinal cord.⁴⁰ This modality provides real-time examination of the spinal tracts at risk during surgical manipulation of the spinal cord. A peripheral stimulus is applied to a distal nerve (the posterior tibial or median nerve). The cephalad progression of the stimulus can be detected along the popliteal fossa, lumbar spine, cervical spine, and cerebral cortex. Stimuli originating from the median nerve generate a detectable signal at Erb's point. The use of anesthetic drugs, in particular high concentrations of volatile inhalation agents, during spinal cord and brainstem surgery can depress SSEP signals. Incremental IV doses or the continuous infusion of a short-acting opioid, such as fentanyl, supplemented with nitrous oxide and/or low-dose isoflurane, may be preferable. SSEP monitoring in pediatric patients appears to be more sensitive to the depressant effects of general anesthesia.⁴¹ Cortical responses were less reliable in children younger than 10 years old and in those with myelodysplasia or cerebral palsy. Although the SSEPs obtained from these patients demonstrated attenuated cortical responses, relatively robust signals were recorded from the cervical spine. The authors recommended that levels of isoflurane and nitrous oxide be maintained below 0.6% and 50%, respectively.

Motor Evoked Potentials

The major drawback of SEP monitoring is that it cannot reliably monitor the integrity of the ventral (motor) pathways. The assessment of motor function is limited by the depressant effect of general anesthetics. In MEP monitoring, magnetic stimulation of the motor cortex with detection of the action potential in the corresponding muscle groups is used to assess motor function. All volatile anesthetic agents, including nitrous oxide, have a dose-dependent depressant effect on MEPs. MEPs appear to be preserved during propofol or dexmedetomidine infusions.^{42,43} However, a dose-dependent attenuation of MEPs appears to occur, and the optimal dosing regimens need to be determined.

Nerve Root Monitoring

Neurosurgical procedures for tethered spinal cord syndrome and spasticity often employ EMG monitoring during identification and dissection of the nerve roots. The tethered spinal cord syndrome resulting from spinal dysraphism is associated with conditions like myelomeningocele, lipoma of the filum terminale, spina bifida occulta, and adhesions from prior spinal surgery. Persistence of this anatomical anomaly can lead to cord or nerve root distortion and impaired perfusion of the spinal cord, with progressive neurologic deficits and chronic pain. The visualization and identification of functional nerve roots may be difficult, so that inadvertent injury can occur during the surgical dissection. This can lead to fecal and urinary incontinence and an exacerbation of lower extremity neurologic dysfunction. EMG monitoring can be helpful for identifying functional nerve roots. Placing EMG electrodes in the external anal and urethral (in girls) sphincters allows continuous monitoring of the nerve roots supplying the pudendal nerves (S2–S4). Inserting a balloon manometer into the bladder and recording changes in pressure during stimulation can assess detrusor muscle



Fig. 82.9 Assessment of motor function during nerve root surgery. Evoked motor responses can be observed through the clear drapes.

function. Movement and evoked action potentials of the anterior tibialis muscle and gastrocnemius and soleus muscles can also be detected visually and by EMG, respectively. Muscle contractions can be readily observed if clear sterile plastic drapes are used (► Fig. 82.9). Muscle relaxation must be discontinued or allowed to dissipate to detect motor activity. Volatile anesthetics and opioids do not appear to interfere with muscle action potentials; the patient should be deeply anesthetized because direct nerve root stimulation often elicits a significant sympathetic response and pain.

Severe spasticity associated with cerebral palsy can be surgically alleviated by a selective dorsal rhizotomy. In this procedure, spasticity is reduced by surgically dividing dorsal rootlets to diminish the afferent input to motor neurons in the spinal cord, thus decreasing the hyperactive reflexes associated with spastic diplegia. Pathologic rootlets are identified by directly stimulating them and noting the corresponding muscle action potential with EMG. Exaggerated action potentials can be elicited in innervated as well as other distal muscle groups. Abnormal rootlets are partially sectioned to decrease afferent nerve conduction. However, the rootlets may contain sensory and proprioceptive fibers.

Another neurophysiologic modality for monitoring spinal cord reflexes is the Hoffmann H-reflex, which is a measure of motor neuron excitability and is significantly increased in children with spastic diplegia. This response can be evoked by directly stimulating the nerve root. The direct efferent muscle response and the Hoffmann reflex are recorded (► Fig. 82.10). The latter represents the reflex potential emanating from the motor neurons of the spinal cord.⁴⁴ Use of the Hoffmann reflex as a guide for measuring the relative degree of spinal reflex hyperactivity during the partial sectioning of pathologic rootlets is more precise. Anesthetic agents limit the utility of the Hoffmann reflex as an intraoperative monitor of spinal reflex activity. Inhalational agents, nitrous oxide, barbiturates, and benzodiazepines all depress the Hoffmann reflex.⁴⁵ The administration of an opioid-based anesthetic with intermittent doses of ketamine or propofol does not appear to suppress the Hoffmann reflex. Because the EMG is the observed end point, muscle relaxation should be avoided

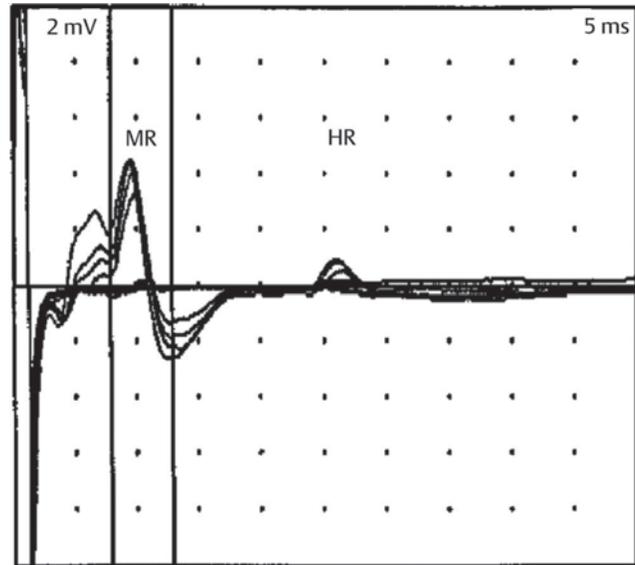


Fig. 82.10 H-reflex. The motor response (MR) occurs at 10 milliseconds, and the H-reflex (HR) follows at 30 milliseconds.

82.4 Postoperative Management

Close observation in an intensive care unit with serial neurologic examinations and invasive hemodynamic monitoring is helpful for the prevention and early detection of postoperative problems. Respiratory dysfunction is the leading complication after posterior fossa craniotomy.⁴⁶ Airway edema is usually self-limited and may require endotracheal intubation as a stent. Occasionally, ischemia or edema of the respiratory centers in the brainstem will interfere with respiratory control and lead to postoperative apnea. Residual narcotics can also produce apnea, but this is transient and can be pharmacologically antagonized with naloxone. Children with Chiari malformations may be more prone to respiratory depression.⁴⁷ Postoperative nausea and vomiting can cause sudden increases in ICP and should be treated with a nonsedating antiemetic. However, the prophylactic administration of ondansetron during surgery has not been effective in decreasing the incidence of vomiting following craniotomies in children.⁴⁸ Although the efficacy of the intraoperative administration of antiemetic drugs as a prophylactic measure is controversial, ondansetron (50 mcg/kg), dexamethasone (0.25 mg/kg), and/or metoclopramide (150 mcg/kg) can be used to treat nausea and vomiting in the postoperative period. Pain control is another issue that complicates the postoperative recovery of patients. Given the sedating effects of analgesic drugs, a delicate balance between pain control and patient responsiveness is essential to allow frequent assessment of the child's neurologic status. One of the most commonly used opioid drugs is morphine. It is administered by the patient's nurse (0.05 to 0.1 mg/kg every 2 to 4 hours) or via patient-controlled infusion pumps in children old enough to cooperate with the technology.

Fluid and electrolyte derangements can occur in the postoperative neurosurgical patient. Serum electrolytes should be measured frequently to detect evolving derangements. Hyponatremia can develop as a consequence of the administration of

hypotonic fluids or the syndrome of inappropriate antidiuretic hormone secretion and can lead to postoperative seizures. Hyponatremia occurs less frequently but should herald the presence of diabetes insipidus or cerebral salt-wasting syndrome. Diabetes insipidus can occur after surgery in the region of the hypothalamus and pituitary gland. The diagnosis can be confirmed by the presence of polyuria (>4 mL/kg per hour), increased serum osmolarity (>300 mOsm/kg), and increased serum sodium (>145 mEq/L). It can be managed acutely with an IV infusion of vasopressin (1 to 5 mU/kg per hour) and the judicious administration of fluid.⁴⁹ Vasopressin has a short half-life and can be titrated to effect (normal urine output, serum osmolality, and sodium concentration). Once the patient is able to tolerate oral intake, vasopressin can be substituted with desmopressin acetate (DDAVP).

Situations may arise in which the patient will require postoperative tracheal intubation and mechanical ventilation. Intraoperative events that most commonly lead to this requirement include neurologic dysfunction and massive blood loss with transfusion. Sedation protocols need to be tailored for the neurosurgical patient to facilitate serial neurologic examinations. Various regimens include midazolam, fentanyl, remifentanyl, and dexmedetomidine infusions. Propofol infusion syndrome has been associated with long-term, high-dose propofol infusion and is characterized by metabolic acidosis, hyperkalemia, rhabdomyolysis, and progressive myocardial failure.⁵⁰ Supportive therapy appears to be the only viable treatment option. Until a controlled prospective analysis of prolonged propofol infusion is performed and the responsible toxin, if one exists, is identified, it is prudent to minimize infusion rates to below 3.0 mg/kg per hour and not to maintain propofol infusions for extensive periods of time.⁵¹

The treatment of postoperative pain is a major component of the perioperative management of the neurosurgical patient. Because most patients who have undergone a craniotomy are observed in a critical care unit, IV opioids (morphine, 0.1 mg/kg IV every 2 to 4 hours as needed) can be carefully titrated to blunt pain, but not to the point of oversedation. Patient-controlled IV opioid infusion pumps can be used by children 7 years old and older; they can also be used by precocious 5-year-olds. Local anesthetics and opioids administered through epidural catheters can provide pain relief for patients who have undergone spine surgery. For patients who are recovering in a less intensive setting, acetaminophen (10 to 15 mg/kg) and codeine (0.5 mg/kg) can be given orally with minimal side effects.

82.5 Special Issues

82.5.1 Neonatal Emergencies

Most neonatal surgery is performed on an emergent basis, which increases risk in the perioperative period.⁵² Congestive heart failure can occur in neonates with large cerebral arteriovenous malformations; this condition requires aggressive hemodynamic support. More commonly, intracardiac right-to-left shunting occurs through a ductus arteriosus or foramen ovale that has not yet closed. Management of the neonatal respiratory system may be difficult because of the diminutive size of the airway, as well as the presence of craniofacial anomalies, laryngotracheal lesions, and acute (hyaline membrane disease,

retained amniotic fluid) or chronic (bronchopulmonary dysplasia) disease. Because these conditions are in a state of flux, they should be addressed preoperatively to minimize perioperative morbidity.

The neonatal CNS is capable of sensing pain and mounting a stress response after a surgical stimulus; therefore, premature infants require anesthesia for painful procedures.⁵³ However, immature neonatal organ systems are highly sensitive to anesthetic agents. Neonatal myocardial function is particularly sensitive to both inhaled and IV anesthetics, and these agents need to be administered judiciously to block the surgical stress response without causing myocardial depression. The administration of an opioid-based anesthetic is generally the most stable hemodynamic technique for neonates. However, the hepatic and renal systems are not fully developed, and neonates anesthetized with a narcotic technique will often have a delayed emergence and may require postoperative mechanical ventilation.

The closure of a myelomeningocele or encephalocele presents special problems. Positioning the patient for tracheal intubation may rupture the membranes covering the spinal cord or brain. Therefore, careful padding of the lesion (► Fig. 82.11) by elevating the neonate on top of soft supports with a hollow center will minimize rupture of the fragile membranes. In some cases, it may be necessary to intubate the trachea with the neonate in the left lateral decubitus position. General anesthesia should be provided to optimize the surgical condition and minimize pain. Most surgical closures of simple myelomeningoceles have relatively minimal blood loss. However, large lesions may require the significant dissection of cutaneous tissue to cover the defect, and these procedures pose greater risks for blood loss and hemodynamic instability. Recent advances in the management of myelomeningoceles have led to early intervention in the intrauterine period.⁵⁴ The management of the fetus and mother during fetal surgery has been reviewed extensively elsewhere.⁵⁵

82.5.2 Craniosynostosis

Remodeling of a craniosynostosis is likely to have the best result if done early in life.⁵⁶ However, these procedures can be

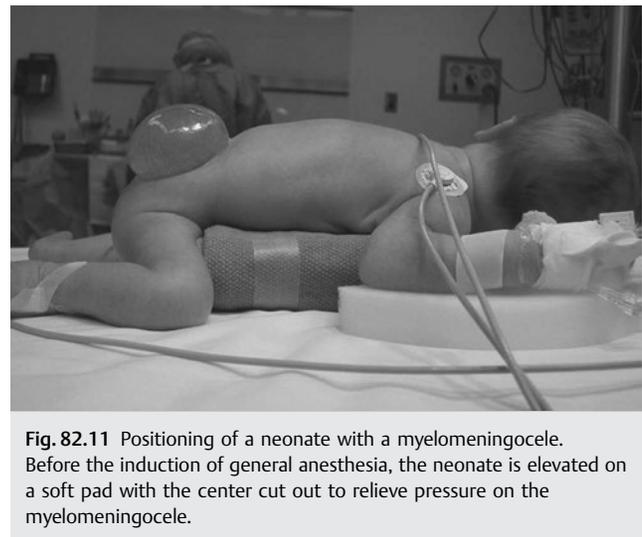


Fig. 82.11 Positioning of a neonate with a myelomeningocele. Before the induction of general anesthesia, the neonate is elevated on a soft pad with the center cut out to relieve pressure on the myelomeningocele.

associated with the loss of a significant percentage of an infant's blood volume, and greater losses occur when more sutures are involved.³³ The use of an antithrombotic drug, such as tranexamic acid, has been shown to reduce blood loss and the need for blood transfusions in pediatric patients undergoing craniotomy surgery.⁵⁷ VAE frequently occur and should be minimized by maintaining adequate intravascular blood volume. Early detection with continuous precordial Doppler ultrasound can make it possible to institute treatment before large amounts of air are entrained. When hemodynamic instability does occur, the operating table can be placed in the Trendelenburg position. This maneuver will augment the patient's blood pressure and prevent the further entrainment of intravascular air. Special risks exist in neonates and young infants because potential right-to-left cardiac mixing lesions can result in the formation of arterial emboli. Minimally invasive techniques in which endoscopy is used for craniotomy repairs have dramatically reduced morbidity in selected patients and reduced the need for invasive anesthetic management.⁵⁸

82.5.3 Tumors

The majority of intracranial tumors in children occur in the posterior fossa; hence, CSF flow is often obstructed and intracranial hypertension and hydrocephalus are often present. Most neurosurgeons approach this region with children in the prone position. The patient's head is generally secured with a Mayfield head frame, although the use of pins in small children can cause skull fractures, dural tears, and intracranial hematomas. Elevation of the bone flap can result in sinus tears, massive blood loss, and/or VAE. The surgical resection of tumors in the posterior fossa can also lead to brainstem and/or cranial nerve damage. ▶ Table 82.9 lists some of the signs of encroachment on these structures. Damage to the respiratory centers and cranial nerves can lead to apnea and airway obstruction after extubation of the patient's trachea. The use of intraoperative magnetic resonance imaging techniques in the pediatric neurosurgical suite presents unique management issues that are justified by the benefits of immediate imaging of the surgical site.⁵⁹ Small children undergoing stereotactically guided radiosurgery require general anesthesia to tolerate the procedure. Special head frames devised to allow airway manipulations should be used in these patients.⁶⁰

82.5.4 Epilepsy

Surgical treatment has become a viable option for many patients with medically intractable epilepsy. Two major considerations should be kept in mind. The long-term administration of

anticonvulsant drugs, such as phenytoin and carbamazepine, induces rapid metabolism and promotes the clearance of several classes of anesthetic agents, including neuromuscular blockers and opioids.⁶¹ Therefore, the anesthetic requirements for these drugs are increased, and close monitoring of their effect and frequent redosing are necessary. Intraoperative neurophysiologic monitors can be used to guide the actual resection of the epileptogenic focus, and general anesthetics can compromise the sensitivity of these devices.⁶² Furthermore, if cortical stimulation is used to mimic the seizure pattern or identify areas on the motor strip, neuromuscular blockade should be antagonized or permitted to abate.

Occasionally, a repeat craniotomy must be performed in a child shortly after the primary procedure. This can be emergent for the evacuation of intracranial hemorrhages. Moreover, an elective repeat craniotomy may be necessary for removal of the ECoG grids and strips used in invasive EEG monitoring and for subsequent resection of the seizure focus. It is important to avoid the administration of nitrous oxide until the dura is opened because intracranial air can persist for up to 3 weeks following a craniotomy, and nitrous oxide in these situations can cause a rapid expansion of air cavities and result in tension pneumocephalus.⁶³

82.5.5 Vascular Anomalies

Vascular anomalies are rare in infants and children. Most are congenital lesions that present early in life. Large arteriovenous malformations in neonates may be associated with high-output congestive heart failure and require vasoactive support. The initial treatment of large arteriovenous malformations often consists of intravascular embolization in the radiology suite.⁶⁴ Operative management is commonly associated with massive blood loss, and patients require several IV access sites and invasive hemodynamic monitoring. Ligation of an arteriovenous malformation can lead to sudden hypertension with hyperemic cerebral edema.⁶⁵ A vasodilator, such as labetalol or nitroprusside, may be necessary to control a hypertensive crisis.

Moyamoya syndrome is a rare, chronic, vaso-occlusive disorder of the internal carotid arteries. It presents as transient ischemic attacks and/or recurrent strokes in childhood. The etiology is unknown, but the syndrome can be associated with prior intracranial radiation, neurofibromatosis, Down syndrome, and a variety of hematologic disorders. The anesthetic management of these patients is directed at optimizing cerebral perfusion.⁶⁶ This includes ensuring generous preoperative hydration and maintaining the blood pressure within the patient's preoperative levels. The maintenance of normocapnia is essential as well because both hyper- and hypocapnia can lead to a

Table 82.9 Effect of surgical manipulation of the brainstem

Brainstem area	Signs	Monitor that is changed
CN V	Hypertension, bradycardia	Arterial pressure, ECG
CN VII	Facial muscle movement	EMG
CN X	Hypotension, bradycardia	Arterial pressure, ECG
Pons, medulla	Arrhythmias, hypo- or hypertension, tachy- or bradycardia, irregular breathing pattern	ECG, arterial pressure, end-tidal carbon dioxide

Abbreviations: CN, cranial nerve; ECG, electrocardiography; EMG, electromyography.

phenomenon of “steal” from the ischemic region and further aggravate cerebral ischemia.⁶⁷ Nitrous oxide and a narcotic-based anesthetic provide a stable level of anesthesia for these patients. EEG monitoring may detect cerebral ischemic events during the intraoperative and postoperative periods.⁶⁸ Once the patient emerges from anesthesia, the same maneuvers that optimize cerebral perfusion should be extended into the postoperative period. These patients should receive IV fluids to maintain adequate cerebral perfusion and should be given adequate narcotics to avoid hyperventilation induced by pain and crying.

82.5.6 Trauma

The management of pediatric head trauma requires a multiple-organ approach to minimize morbidity and mortality.⁶⁹ A small child's head is often the point of impact in injuries, but other organs can also be damaged. Basic life support algorithms should be immediately applied to ensure a patent airway and adequate respiration and circulation. Because the head-to-torso ratio is large in infants and younger children, acceleration-deceleration injuries are more common in the pediatric population and lead to diffuse injuries of the brain and upper cervical spine. Immobilization of the cervical spine is important to avoid secondary spinal cord injury with manipulation of the patient's airway until radiologic clearance is confirmed. Therefore, a patient with an unstable cervical spine should be immobilized with cervical traction during a laryngoscope procedure for tracheal intubation. Blunt abdominal trauma and long-bone fractures frequently occur together with head injury and can be major sources of blood loss. To ensure tissue perfusion during the operative period, the patient's blood volume should be restored with crystalloid solutions and/or blood products. Ongoing blood loss can lead to coagulopathies and should be treated with specific blood components.

Infants with shaken baby syndrome often present with chronic or acute subdural hematomas.⁷⁰ As in all patients who have sustained trauma, coexisting injuries, fractures, and abdominal trauma should be identified. Small children undergoing a craniotomy for the evacuation of an epidural or subdural hematoma are at risk for significant blood loss and VAE. The postoperative treatment of these victims includes the management of intracranial hypertension and, in the most severe cases, a determination of brain death.

The management of pediatric head injury is currently based on a few randomized trials and draws heavily from data derived from adult series; evidence-based management is still evolving. Therefore, a fundamental knowledge of the age-related differences in cerebrovascular physiology and anatomy is essential in the application of adult-based protocols for head trauma in pediatric patients. A multispecialty group of pediatric neurosurgeons and intensivists have published “Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents—Second Edition.”⁷¹ This provides a comprehensive, evidence-based review of controversial management issues in the care of the pediatric patients with head injuries. The goals of therapy should be based on the data obtained from cerebrovascular monitors. Maintaining the cerebral perfusion pressure above 40 mm Hg appears to be associated with the best outcome in pediatric patients. However, studies in infants need to be performed to assess the safety of

even a lower cerebral perfusion pressure. Patients with severe intracranial hypertension, which is refractory to these medical maneuvers, may warrant surgical decompression of hemorrhagic and edematous brain tissue, which may play a role in the management of some infants and children with severe head injuries.⁷² The same principles used for the intraoperative management of patients undergoing craniotomies should be applied in this situation.

82.5.7 Spine Surgery

Spinal dysraphism is the primary indication for laminectomies in pediatric patients. Many of these patients have a history of a meningomyelocele closure followed by several corrective surgeries. They have been exposed to latex products and frequently develop hypersensitivity to latex. Latex allergy can manifest with a severe anaphylactic reaction, heralded by hypotension and wheezing with or without a rash. It should be rapidly treated with removal of the source of the latex and the administration of fluid and vasopressors.⁷³ Patients at risk for latex allergy should be managed in a latex-free environment.

Tethered cord release entails EMG monitoring to help identify functional nerve roots. EMG of the anal sphincter and muscles of the lower extremities is performed intraoperatively to minimize inadvertent injury to the nerves innervating these muscle groups.⁷⁴ Neuromuscular blockade should be discontinued or antagonized to allow accurate EMG monitoring. An epidural catheter inserted by the surgeon under direct vision can provide a conduit for the administration of local anesthetics and opioids for the management of postoperative pain.

82.5.8 Neuroendoscopy

Technological advances in minimally invasive endoscopic surgery have entered the neurosurgical arena. The anesthetic considerations for these evolving techniques are the same as those for any of the other neurosurgical procedures discussed in this chapter.⁷⁵ Because neuroendoscopic techniques are designed to minimize surgical incision, dissection, and blood loss, less aggressive fluid replacement and less invasive hemodynamic monitoring are becoming the norm. Endoscopic strip craniectomy in neonates and infants is associated with decreases in blood loss, surgical time, VAE, and postoperative recovery time.^{58,76–78} Endoscopic third ventriculostomy has become an accepted procedure for the treatment of obstructive hydrocephalus in infants and children.⁸⁰ Despite the relative safety of this procedure, bradycardia, other arrhythmias, and neurogenic pulmonary edema have been reported in conjunction with the use of irrigation fluids (especially when cold) and/or manipulation of the floor of the third ventricle.^{81,82}

82.5.9 Neuroradiology

Recent advances in imaging technology have made it possible to use less invasive procedures to diagnose and treat lesions in the CNS. Most neuroradiologic studies, such as computed tomography and magnetic resonance imaging, can be accomplished with light sedation. Recommendations have been published by consensus groups of anesthesiologists and pediatricians and can serve as guidelines for managing these patients.⁸³

⁸⁴ General anesthesia is typically used for uncooperative patients, patients with coexisting medical problems, and for those undergoing potentially painful procedures, such as intravascular embolization of vascular lesions.⁶⁴

82.6 Summary

The perioperative management of pediatric neurosurgical patients presents an array of challenges to neurosurgeons and anesthesiologists. Many conditions are unique to small children. Thorough preoperative evaluation and open communication between members of the health care team are important. A basic understanding of age-dependent variables and the interaction of anesthetic and surgical procedures is essential in minimizing perioperative morbidity and mortality.

Pearls

- A thorough preoperative organ system–based evaluation of the pediatric patient is essential to minimize perioperative morbidity.
- A larger percentage of the neonate's and infant's cardiac output is diverted to the head. As a result, the patient is exposed to hemodynamic instability during neurosurgical procedures.
- IV and arterial access should be established and secured before the operation because these patients are frequently inaccessible during surgery.

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